The use of lipid-based nanocarriers for targeted pain therapies

Susan Hua1 * and Sherry Y. Wu2

1 School of Biomedical Sciences and Pharmacy, The University of Newcastle, Callaghan, NSW, Australia
2 Department of Gynecologic Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

INTRODUCTION

Targeted drug delivery provides effective, precise, and safe therapeutic interventions for treatments of diverse disease conditions, by limiting toxic side effects and/or increasing drug action. Effective drug targeting depends on several factors that are either carrier or target related. The drug carrier must be stable, protect the drug from degradation, protect the body from harmful side effects, and allow delivery to the target cell population in vivo (Koning et al., 2002). The target must be well accessible for the drug-targeting system and must display specific cell-surface molecules that allow selective targeting and efficient drug delivery (Vingerhoeds et al., 1994; Willis and Forssen, 1998; Ding et al., 2006). The field of site-specific drug delivery has been continuously explored to develop formulations with a therapeutically acceptable degree of target specificity. Many different approaches using various physical and biochemical principles have been proposed and examined, with targeted liposomes as a carrier for both hydrophobic and hydrophilic drugs having attracted much attention.

LIPOSOMES AS DRUG DELIVERY CARRIERS

Liposomes have long been considered good candidates for efficient drug carrier and delivery systems. They have been used as delivery vehicles for stabilizing drugs, overcoming barriers to cellular and tissue uptake, and for directing their contents toward specific sites in vivo (Senior, 1987; Oku and Namba, 1994; Vingerhoeds et al., 1994; Woodle et al., 1996; Torchilin, 1994; Willis and Forssen, 1998; Bendas, 2001; Maruyama, 2002; Moghimi and Szebeni, 2003; Metselaar and Storm, 2005; Ding et al., 2006). The unique ability of liposomes to entrap drugs both in an aqueous and a lipid phase make such delivery systems attractive for hydrophilic and hydrophobic drugs. Hydrophobic molecules can be entrapped in the internal aqueous region. Additionally, by virtue of their large aqueous interior and biocompatible lipid exterior, they offer a possible means of local delivery of a large variety of drug structures, from small molecules to macromolecules such as proteins and DNA, to the site of interest while reducing systemic toxicity (Senior, 1987; Oku and Namba, 1994; Torchilin, 1994; Laverman et al., 1999; Ulrich, 2002; Sahoo and Labhasetwar, 2003). In vivo behavior of liposomes can be easily modified by changing their characteristics, such as size, lipid composition, and charge (Senior, 1987; Oku and Namba, 1994; Willis and Forssen, 1998; Laverman et al., 1999; Ulrich, 2002). In addition, the liposome surface can be modified with polymer structures such as poly(ethylene glycol) (PEG), which inhibits macrophage uptake and thereby increases liposome circulation time, and with targeting moieties such as antibodies or peptides (Senior, 1987; Oku and Namba, 1994; Torchilin, 1994; Woodle et al., 1994; Maruyama, 2002; Moghimi and Szebeni, 2003). Site-directing ligands incorporated into the liposome membrane surface therefore have been investigated intensely in an effort to further enhance the selectivity of liposomal drug delivery (Sawant and Torchilin, 2012; Allen and Cullis, 2013; Koshkaryev et al., 2013). Unlike solid polymeric carrier systems, liposome membranes are dynamic structures, allowing surface-coupled ligands a greater degree of freedom with the ability to move about hydrophilic molecules within the bilayer membrane, and

Sustained delivery of analgesic agents at target sites remains a critical issue for effective pain management. The use of nanocarriers has been reported to facilitate effective delivery of these targets to sites while minimizing systemic toxicity. These include the use of biodegradable liposomal or polymeric carriers. Of these, liposomes present as an attractive delivery system due to their flexible physicochemical properties which allow easy manipulation in order to address different delivery considerations. Their favorable toxicity profiles and ease of large scale production also make their clinical use feasible. In this review, we will discuss the concept of using liposomes as a drug delivery carrier, their in vivo characteristics as well as in vivo behavior. Current advances in the targeted liposomal delivery of analgesic agents and their impacts on the field of pain management will be presented.

Keywords: pain, inflammation, liposomes, nanocarriers, targeted drug delivery
within the bilayer plane, positioning themselves for optimal sub-
strate interactions (Willis and Forssen, 1998). Critical factors for
successful in vivo delivery of ligand-targeted liposomes will
involve selection of accessible and appropriate targets, use of lig-
ands with adequate selectivity and affinity for these targets, and
suitable liposome surface coupling methods for correct presen-
tation of ligands to their binding sites (Vingerhoeds et al., 1994;
Torchilin, 1996; Willis and Forssen, 1998; Metelsaar and Storm,
2005; Ding et al., 2006). The benefit of liposomes as therapeutic
carriers stimulates the accumulation of novel experiences in the
practical aspects of liposomes, as well as new developments in basic
research.

**IN VIVO STABILITY, BIODEISTRIBUTION, AND
BIOSABILITY OF LIPOSOMES**

Several major hurdles must be overcome in order to prolong
liposome circulation times. These include stabilizing the vesi-
cles against leakage of entrapped contents, avoiding opsonization,
and minimizing removal by the reticuloendothelial system (RES;
Willis and Forssen, 1998). The rate at which liposomes are cleared
depends on their size, surface charge, and stability (Oku and
Namba, 1994; Laverman et al., 1999; Ishida et al., 2001; Ulrich,
2002). The presence of a high electrostatic surface charge pro-
motes the interaction of liposomes with biomolecules that could
serve as opsonins and with cells (Laverman et al., 1999; Ishida et
al., 2001). In general, unmodified large liposomes are cleared more
rapidly than small, neutral, or positively charged liposomes (Oku
and Namba, 1994; Laverman et al., 1999; Ishida et al., 2001; Ulrich,
2002). Previous studies have demonstrated that the liver removes
large, charged liposomes rapidly, with spleen clearance half-life
of less than 1 h (Chrai et al., 2002). The presence of cholesterol is
another important factor both for enhancing stability against leak-
age and in minimizing phospholipid exchange (Willis and Forssen,
1998; Laverman et al., 1999). This minimizes lipid exchange with
other structures in the circulation (red blood cells, lipoproteins),
which can lead to depletion of the high phase transition tempera-
ture lipids and their replacement with less physiologically stable
components (Willis and Forssen, 1998; Laverman et al., 1999;
Ulrich, 2002).

A major concern in using liposomes for therapeutic purposes
is their fast removal from blood circulation by components of the
RES. The RES is the major site of liposome accumulation after sys-
temic administration. Primary organs associated with the RES are
the liver, spleen, kidneys, lungs, bone marrow, and lymph nodes
(Senaste, 1987; Oku and Namba, 1994; Vingerhoeds et al., 1994;
Ishida et al., 2001; Chrai et al., 2002). The liver exhibits the largest
capacity for uptake, whereas the spleen can accumulate liposomes
so that its tissue concentration is 10-fold higher than those of other
organs (Chrai et al., 2002). Removal of liposomes from the blood is
attributed to phagocytic cells that reside in the RES and is mediated
through direct interactions between those cells and the liposo-
mes (Senior, 1987; Oku and Namba, 1994; Vingerhoeds et al.,
1994; Ishida et al., 2001; Chrai et al., 2002). Although clearance
of liposomes by the RES occurs predominantly after opsoniza-
tion of the vesicles, that is the adsorption of plasma proteins
(e.g., immunoglobulins, fibrinogen, complement components,
C-reactive protein) onto their surface, in vitro studies have shown
that liposomal uptake into macrophages can also occur in the
absence of serum proteins (Ishida et al., 2001; Chrai et al., 2002).
The extent of opsonization decreases with a decrease in liposome
size from 800 to 200 nm in diameter (Chrai et al., 2002). Small
liposomes could not support opsonic activity, whereas the larger
ones did so substantially. The profound effect of size on comple-
ment recognition affects liver uptake, depending on the extent of
liposome opsonization (Laverman et al., 1999; Ishida et al., 2001;
Chrai et al., 2002). One of the major steps in improving circulation
time and preventing removal by RES was sterically-stabilizing the
liposomes through the introduction of PEG modification (Oku
and Namba, 1994; Torchilin, 1994, 1996; Vingerhoeds et al.,
1994; Woodle et al., 1994; Willis and Forssen, 1998; Maruyama,
2002; Ulrich, 2002; Moghimi and Szleheni, 2003). More specifically,
stabilization of liposomes with PEG creates a local surface con-
centration of highly hydrated groups which sterically inhibits both
electrostatic and hydrophobic interactions with a variety of serum
proteins or cells, thus resulting in a reduced uptake by cells of the
RES (Ishida et al., 2001). Many targeting systems with promising
outlook based on in vitro results have faced the above problems
when tested in vivo (Sahoo and Lahbassem, 2003). Therefore,
having an understanding of the events that take place in vivo
is essential for the design of particles with optimal circulation
profiles.

The accumulation of liposomes at the target site is a prerequi-
site but does not necessarily guarantee a therapeutic effect of the
capsulated drug. Therefore, the crucial role of the liposome-cell
interaction has to be taken into account (Vingerhoeds et al., 1994;
Willis and Forssen, 1998; Ulrich, 2002). Multiple factors such as
activation state of the target cell or size, charge, sterical stabiliza-
tion, and pH-dependence of the liposomes have an important
impact on this interaction (Vingerhoeds et al., 1994; Willis and
Forssen, 1998; Laverman et al., 1999; Ulrich, 2002; Muro and
Myuykantov, 2005). The cellular incorporation of liposomal con-
ten can occur in different ways: (i) extracellular release of the
soluble content and uptake via diffusion or pore formation; (ii)
liposomal fusion within the cell membrane followed by an intra-
cellular release of the liposomal content; and (iii) active uptake
of the liposomes via an endocytic or phagocytic pathway
(Vingerhoeds et al., 1994; Willis and Forssen, 1998; Bendas,
2001; Ulrich, 2002). In receptor-mediated endocytosis, small particles
(<150 nm diameter) bind to cell surface receptors and are taken
up by clathrin-coated pits to form coated vesicles. After internal-
ization, the clathrin coat is removed and the vesicle fuses with
lysosomes, which induces the breakdown of the lipids and release
of their contents. Large particles (>150 nm), on the other hand,
are taken up principally by phagocytosis, which is usually limited
to specific cells such as macrophages but can be induced in many
other cell types with appropriate ligands. In both cases, liposomes
could either be degraded in the low pH environment, or they
could fuse directly with the endosomal or lysosomal membrane
(Willis and Forssen, 1998; Ulrich, 2002). In addition, macro-
nuclei can cross the endothelial barrier in three ways (Koning
et al., 2002) between the cells, through cell junctions (paracellu-
lar); (Ding et al., 2006) through the endothelial cell, via pores;
and (Vingerhoeds et al., 1994) transcellularly, via shuttling vesicles
and specific receptors (van Hinsbergh, 1997; Antohe et al., 2004).

Frontiers in Pharmacology | Neuropharmacology
November 2013 | Volume 4 | Article 143 | 2

“fphar-04-00143” — 2013/11/20 — 16:41 — page 2 — #2
It is generally believed that the charge and compactness of the endothelial matrix contribute additionally to the selectivity of the endothelial barrier toward molecules of different size and charge (van Hinsbergh, 1997).

**LIPOSOMES – THERAPEUTIC OPPORTUNITIES**

The use of liposomes as drug sustained release systems or as drug delivery systems for passive targeting is well established, with several drug formulations in the clinic or in late clinical trials (Sawant and Tschöke, 2012; Allen and Cullis, 2013; Koshikaryev et al., 2013). Several laboratories have reported the use of liposomes as drug carriers in the treatment of cancer, fungal diseases, and inflammatory or immune diseases (Oku and Namba, 1994; Vingerhoeds et al., 1994; Woodle et al., 1994; Willis and Forsgren, 1998; Sahoo and Lahbabetwar, 2003; Metelskaar and Storm, 2005). Innovative research in liposomal drugs has led to commercialization of several liposomal formulations, including anticancer therapeutics (Doxil™ and Myocet™) and an antifungal drug formulation (AmBisome™). These products have demonstrated improved therapeutic indices over their corresponding conventional drugs by avoiding sensitive tissues and/or increasing delivery to specific targets in vivo (Oku and Namba, 1994; Vingerhoeds et al., 1994; Willis and Forsgren, 1998). Liposomes offer several advantages over other delivery systems including biocompatibility, capacity for self-assembly, ability to carry large payloads of active agent, and a wide range of physical properties that can be modified to control their biological properties (Senior, 1987; Woodle et al., 1994; Tschöke, 1996; Willis and Forsgren, 1998; Bendas, 2001; Moghimi and Szczepan, 2003). Additionally, the delivery system itself is pharmacologically inactive with minimal toxicity, and is readily metabolized and cleared from the circulation once its carrier function has been completed (Willis and Forsgren, 1998). An advantage that liposomes possess over solid particulate delivery systems is their ability to transport and deliver biologically active molecules without the need for covalent coupling (Willis and Forsgren, 1998).

To improve upon these therapies, clinically active liposomal delivery systems may need to include site-directed surface ligands to further enhance their selective delivery. The concept of drug targeting and controlled drug delivery is used in attempts to improve the therapeutic index of drugs by increasing their localization to specific organs, tissues, or cells and by decreasing their activity and potential toxic side effects in normal organs (e.g. heart, liver, or kidneys). This concept is especially important for drugs with a narrow therapeutic window which has the potential of having detrimental effects (Vingerhoeds et al., 1994; Willis and Forsgren, 1998; Bendas, 2001; Maruyama, 2002).

**USE OF NANOCARRIERS FOR PAIN THERAPIES**

Drug delivery systems have been used in pain therapies to improve toxicity or side effect profiles by targeted delivery to specific sites in the body, increase drug upload or bioavailability, and to provide prolonged drug release. For example, an area of interest has been the delivery of opioid-based compounds to target peripheral opioid receptors within injured tissue to promote analgesic and anti-inflammatory activity (Hua and Cabot, 2010). It is well-established that many conventional opioid agonists have been shown to produce potent opioid receptor mediated analgesia when administered locally into injured tissue of rodents, non-human primates, and humans (Stein et al., 2001, 2003; Rittner and Stein, 2005; Rittner et al., 2005). However, with increased blood flow secondary to inflammation, drugs may still be absorbed into the systemic circulation, leading to side effects mediated by activation of central or peripheral opioid receptor activity (e.g., sedation, respiratory depression, dependence, tolerance, nausea, or constipation) (Stein et al., 2001, 2003; Menendez et al., 2005; Rittner et al., 2005; Rittner and Stein, 2005; Sevostianova et al., 2005). This area of research of applying targeted drug delivery and the use of nanocarriers in the management of pain is a novel and exciting area of research, with much potential for growth and clinical benefits. The remainder of the review will focus on the progress made in this area of research in experimental and clinical studies (Figure 1).

**EXPERIMENTAL USE OF NANOCARRIERS FOR PAIN THERAPIES**

Nanosystems used for delivering compounds intended for pain therapies, such as local anesthetics (de Paula et al., 2012) or non-steroidal anti-inflammatory drugs (NSAIDs), have been reviewed previously (Puglia et al., 2013). The encapsulation of local anesthetics into liposomes, for instance, presents advantages such as slow release, prolonged duration of action, reduced plasma concentrations, and low toxicity to the central nervous and cardiovascular systems. A number of pre-clinical studies have been conducted encapsulating local anesthetics, such as bupivacaine or lidocaine, into multilamellar or unilamellar liposomes using different phospholipid and pH combinations (de Paula et al., 2012). These studies report increased duration of anesthesia and sensory blockade following parenteral administration of these formulations.

Targeted delivery of glucocorticosteroids has been widely studied for the treatment of rheumatoid arthritis and other inflammatory joint conditions (Metelskaar et al., 2003, 2004; Metelskaar and Storm, 2005). Although corticosteroids are not classified as an analgesic, the pain relieving effects are secondary to their anti-inflammatory activity. Long-circulating PEGylated liposomes containing methylprednisolone or betamethasone have been used to treat Lewis rats with adjuvant-induced arthritis (AIA) both at early (before clinical signs appear) and late (at the peak of the disease) stages of the disease (Avnir et al., 2008). In addition, Ulmansky et al. (2012) showed that intravenous treatment with sterically stabilized nano-liposomes (NSL) encapsulated with methylprednisolone or betamethasone significantly decreased the severity of adjuvant arthritis in Lewis rats throughout all disease stages. They reported that both subcutaneous and intravenous administration of glucocorticoid-encapsulated NSL was able to suppress arthritis significantly compared to higher doses of the free drugs or to TNF-α antagonists (Ulmansky et al., 2012).

Non-steroidal anti-inflammatory drugs have long been used as an analgesic and anti-inflammatory agent. However, they are associated with numerous interactions with other medications and have serious side effects to the gastrointestinal tract, kidneys, and cardiovascular system (Rittner et al., 2005; Warner and Mitchell, 2008). Nanocarriers have been used to enhance the efficacy and reduce the toxicity of NSAIDs by targeted delivery to...
the site of inflammatory pain. A number of topical and parenteral nano-formulations have been utilized and have shown success in preclinical studies (Bansal et al., 2007; Raffin et al., 2012; Tarjou et al., 2012; Dong et al., 2013; Puglia et al., 2013). Dong et al. (2013) recently demonstrated that celecoxib-loaded liposomes embedded into hyaluronate gel was more effective than either single agent in pain control and cartilage protection in a rabbit knee osteoarthritismodel following intra-articular injection.

Targeted nanoparticles have recently been engineered to deliver opioids, in particular loperamide HCl, specifically to peripheral opioid receptors to induce analgesic and anti-inflammatory actions for use in painful inflammatory conditions (Hua and Cabot, 2013). Loperamide is a peripherally-selective mu-opioid receptor agonist that does not have analgesic effects following intravenous or oral application due to its physicochemical properties. These nanoparticles are conjugated with antibodies targeted against intercellular adhesion molecule-1 (anti-ICAM-1) which mimics the properties of opioid-containing immune cells. These targeted nanoparticles produced highly significant analgesic and anti-inflammatory effects over the 48-h time course studied following intravenous administration in rats with Complete Freund’s Adjuvant-induced inflammation of the paw. Biodistribution data demonstrated specific localization of the targeted nanoparticles to peripheral inflammatory tissue with no significant uptake into the brain (Hua and Cabot, 2013). Other sustained release systems have also been engineered to prolong the duration of action of opioid analgesics (Ward et al., 2013).

A number of non-lipid-based nanocarrier formulations have also been studied to improve the oral (Martín-Banderas et al., 2012; Tang et al., 2012), intranasal (Kumar et al., 2013; Patel et al., 2013), and CNS delivery of analgesic agents (Liu et al., 2006; Tosi et al., 2007; Chen et al., 2013). Local or systemic administration of endogenous opioid peptides (e.g. β-endorphin) is not viable due to its short half-life in the blood and within inflamed tissue. Liu et al. (2006) demonstrated that opioid peptides, in particular endomorphin-1, adsorbed onto the surface of butylcyanoacrylate nanoparticles and coated with polysorbate 80 could penetrate the blood-brain barrier following intravenous administration to cause analgesia. Tosi et al. (2007) investigated the in vivo antinociceptive efficacy of peptide-derivatised nanoparticles loaded with loperamide HCl for delivery to central opioid receptors, and reported a peak percentage of maximum possible effect (% MPE) of 60% at 4 h and a significant sustained release effect for 6 h after tail vein injection of a dose equivalent of 0.7 mg of loperamide HCl in Wistar rats. In addition, Chen et al. (2013) showed that nanoparticles consisting of loperamide and PLGA-PEG-PLGA triblock copolymer coated with poloxamer 188 or polysorbate 80 had improved penetration
across the blood-brain barrier in comparison to PLGA-PEG-PLGA nanoparticles and PLGA nanoparticles. These studies demonstrate that the use of surface modification for nanoparticles is an efficient strategy to deliver opioid analgesics to specific sites in the body.

**CLINICAL USE OF NANO CARRIERS FOR PAIN THERAPIES**

Although liposomes and nanoparticles present an exciting opportunity to improve the management of a variety of painful conditions, current clinical use is limited and few products appear to be in use for human clinical trials. Liposome encapsulation of local anesthetics, NSAIDs, and opioids has been studied in humans with promising results. For example, liposomal formulations of local anesthetics have been demonstrated to provide significantly prolonged pain relief after surgical procedures and in chronic cancer (de Paula et al., 2012). Gornek et al. (2011) compared the magnitude and duration of postoperative analgesia from a single dose of bupivacaine extended-release injection with placebo administered intraoperatively via wound infiltration in 184 patients undergoing hemiorthoscopic in a multicenter, randomized, double-blind, placebo-controlled trial. The results showed that the liposomal formulation significantly reduced pain over 72 h and decreased opioid requirements, compared to placebo (Gornek et al., 2011). Similarly, Lafont et al. (1996) reported prolonged pain relief in a patient with chronic cancer that lasted for 1 h after injection of a liposomal bupivacaine formulation, compared to 4 h for plain bupivacaine.

The efficacy of topical liposomal NSAID-based formulations has also been demonstrated in clinical studies (Puglia et al., 2013). For example, indomethacin-loaded liposomes incorporated into hydrogels were studied in UVB-induced erythema on healthy human volunteers. The results provided a more prolonged anti-inflammatory effect in comparison to a gel formulation containing free drug, allowing a sustained release of the drug to deeper skin layers (Puglia et al., 2004).

Strategies to restrict the access of opioid agonists to the CNS have also been of major interest in pain research (Menendez et al., 2005; Severyanova et al., 2005). With regards to incorporation of hydrophilic opioids into liposomal formulations, an extended-release morphine preparation based on a multivesicular lipid suspension foam technology is available in the United States (Rose et al., 2005; Viscusi et al., 2005). This preparation is indicated for pain relief after major surgery (e.g., orthopedic surgery involving lower extremities, lower abdominal surgery, or cesarean delivery) as a single lumbar epidural injection. Studies have demonstrated effective, dose-related analgesia for up to 48 h after a single dose (Rose et al., 2005; Viscusi et al., 2005). Although the safety profile was largely consistent with those for other epidurally administered opioid analgesics, systemic adverse effects were still reported. In fact, the rate of respiratory depression was higher in the liposomal morphine group compared with the intravenous patient controlled analgesia (PCA) fentanyl group, which suggest that patient characteristics are important in choosing an appropriate dose of liposomal morphine (Viscusi et al., 2005). While benefits were seen with its use following cesarean section (Carvalho et al., 2007), another study showed no benefit over traditional opioids following abdominal surgery with breakthrough pain relief still required and a similar side effect profile to traditional opioids (Gambling et al., 2005). To date, the clinical studies for pain therapies have only investigated the use of conventional liposomes which permits passive targeting. It is anticipated that the use of ligand-targeted nanocarriers (active targeting) for pain therapies will further improve the efficacy and side effect profile of the conventional liposome formulations.

**CONCLUSION**

This phenomenon of disease-site targeting is believed to play a major role in the enhanced efficacy observed for a variety of drugs when formulated inside lipid vesicles. Despite the clinical need, the use of nano-based therapeutics to target and treat inflammation and pain is only beginning to be exploited. The use of drug-loaded liposomes for this application would be promising for a multitude of acute and chronic pain conditions (e.g., post-operative pain, visceral cancer pain, rheumatoid arthritis, or neuropathic pain). Their use will ultimately lead to improved efficacy, increased duration of action, and improved side effect profile of analgesic and anti-inflammatory therapeutics.

**ACKNOWLEDGMENT**

This work was supported by The Pharmacy Research Trust of New South Wales.

REFERENCES

Allen, T. M., and Cullis, P. R. (2013). Liposomal drug delivery systems: from concept to clinical applications. Adv. Drug Deliv. Rev. 65, 36–48. doi: 10.1016/j.addr.2012.09.017

Antoine, F., Liu, L., Rao, G. Y., Pumolly, M. J., and Allen, T. M. (2004). Transdermal movement of liposomes in vitro mediated by cancer cells, neutrophils or hormones. J. Liposome Res. 14, 1–25. doi: 10.1081/LPR-120036990

Arini, Y., Ulmansky, R., Wasserman, V., Even-Chen, S., Boyer, M., Bareloko, Y., et al. (2003). Amphiphilic weak acid glucocorticoid prodrugs remote-loaded into sterically stabilized nanoliposomes evaluated in arthritic rat and in a Beagle dog: a novel approach to treating autoimmune arthritis. Arthritis Rheum. 50, 119–129. doi: 10.1002/art.15342

Bunel, S. S., Joshi, A., and Rumal, A. K. (2007). New dosage formulations for targeted delivery of cyclo-oxygenase-2 inhibitors: focus on use in the elderly. Drugs Aging 24, 441–453. doi: 10.1165/0898542114294952

Bendas, G. (2011). Intraliposomes: a promising approach to targeting cancer therapy. BioDrugs 25, 215–224. doi: 10.2165/00063030-201025040-00002

Carvalho, B., Roland, L. M., Chiu, L. F., Campbell, V. A., and Riley, E. T. (2007). Single-dose, extended-release epidural morphine (DepoDur) compared to conventional epidural morphine for post-caesarean pain. Anesth. Analg. 105, 176–183. doi: 10.1213/ane.0b013e3180616f38

Chen, V. C., Hsiao, W. Y., Lee, W. F., and Zeng, D. T. (2013). Effects of surface modification of PLGA-PEG-PLGA nanoparticles on loperamide delivery efficiency across the blood-brain barrier. J. Biomed. Mater. Res. Part B: Appl. Biomater. 101, 809–822. doi: 10.1002/jbmr.21425

Chin, S. S., Mover, K., and Ahsal, I. (2002). Liposomes (a review) part two. Drug delivery systems. BioPharm 17, 40–43.

de Paula, E., Cereola, C. M., Franca, J. F., de Araujo, D. R., Franco-Montan, M., Tolfo, G. B., et al. (2012). Micro and nanoparticles for delivering local anesthetics. Expert Opin. Drug Deliv. 9, 1905–1924. doi: 10.1517/17425247.2012.738864

Drug, B. S., Dutahla, T., Seshan, V. V., Meno, S., and Murukumar, V. R. (2006). Advanced drug delivery systems that target the vascular endothelium. Mol. Interv. 6, 98–112. doi: 10.1124/mi.6.2.7

Dong, J., Jiang, D., Wang, Z., Wu, G., Miao, L., and Huang, L. (2013). Intraretinal delivery of liposomal calcitriol-1,25-dihydroxate combination for the treatment of osteosarcoma in rabbit model. Int. J. Pharm. 441, 285–290. doi: 10.1016/j.ijpharm.2012.11.031
Puglia, C., Trneci, G. G., and Bonina, F. (2015). Emerging role of collodion drug delivery systems (CDDS) in NSAIAD topical administration. Curr. Med. Chem. 20, 1847–1857. doi: 10.2174/10222904118013438

Roth, P. L., Lima, A., Lorenzoni, R., Antonov, M. B., Tiara, C., Abou, M. F., et al. (2012). Natural lipid nanoparticles containing nimesulide: synthesis, characterisation and in vivo antiinflammatory and antiphototoxic activities. J. Biomol. Nucleic Acids 39, 319–325. doi: 10.1016/j.jbna.2012.05.037

Rittner, H. L., and Stein, C. (2005). Involvement of cytokines, chemokines and adhesion molecules in opioid analgesia. Eur. J. Pain 9, 109–112. doi: 10.1016/j.ejpain.2004.08.009

Rittner, H. L., Machida, H., and Stein, C. (2005). Leukocytes in the regulation of pain and analgesia. J. Leukoc. Biol. 78, 1239–1252. doi: 10.1016/j.jlb.2005.08.004

Rose, J. S., Neil, J. M., and Kopacz, D. J. (2005). Extended-duration analgesia update on microspheres and liposomes. Reg. Anesth. Pain Med. 30, 275–289.

Sahos, S. R., and Lahittebauer, V. (2003). Nanotarget approaches to drug delivery and imaging. Drug Discov. Today 8, 1125–1130. doi: 10.1016/S1359-6446(03)02905-2

Sawant, B. R., and Torchilin, V. P. (2012). Challenges in development of targeted liposomal therapeutics. AAPS J. 14, 351–355. doi: 10.1208/s12248-012-9350-3

Smic, J. H. (1987). Fate and behavior of liposomes in vivo: a review of controlling factors. Crit. Rev. Ther. Drug Carrier Syst. 3, 123–193.

Srivastava, N., Dayne, W., and Bopeal, A. Y. (2005). Analogic effects of morphine and loperamide in the rat formalin test: interactions with NMDA receptor antagonists. Curr. Pharm. Des. 523, 85–90. doi: 10.1016/j.ejphar.2005.10.010

Stein, C., Machida, H., and Schuetz, M. (2001). Peripheral analgesic and antiinflammatory effects of opioids. Z. Rheumatol. 60, 416–424. doi: 10.1007/s003930170084

Torchilin, V. P. (2003). Infiltration liposomes. Nanotechnology 14, S87–S96. doi: 10.1088/0957-4484/14/12A/103

Torchilin, V. P. (1994). Intracellular and intercellular liposomes: possible use for targeted delivery of imaging agents. J. Control Release 34, 285–289. doi: 10.1016/0168-3659(94)90088-7

Torchilin, V. P. (1998). Inhibitory effects of liposomes on MRC-9 and A673 cell adhesion molecules. Cytotechnology 26, 41–49. doi: 10.1007/bf02757891

van de Water, M. E., van der Schans, C. P., Mantzarlis, M., Looijenga, H. L., van der Burg, M. H. A., and de Vries, E. G. (2011). Liposomes as potential therapeutic carriers for HIV-1: a review. J. Control Release 151, 170–185. doi: 10.1016/j.jconrel.2011.01.004

Van Hinsbergh, W. V., van Lingen, A., and Smits, G. (2004). Liposomes for targeting and dosing of small molecules. J. Control Release 95, 197–218. doi: 10.1016/j.jconrel.2003.09.008

Viscusi, E. R., Martin, G., Hartrick, C. T., Singla, N., and Manvelian, G. (2005). A novel, extended-release epidural morphine formulation. Pain Physician. 8, E199–E216. doi: 10.1097/DCR.0b013e318232d4c1

Voon, E. C., Martin, G., Harris, C. T., Singh, N., and Manvelian, G. (2005). Forty-eight hours of postoperative pain relief after total hip arthroplasty with a novel, extended-release epidural morphine formulation. Anesthesiology 102, 1013–1022. doi: 10.1097/01.anes.0000180550.000022

Waltemire, D. S., Yang, D., Lin, A., and Bhatia, S. N. (2005). Long-circulating liposomes in antiinflammatory therapy. J. Leukoc. Biol. 77, 224–232. doi: 10.1007/s00317-005-0879-9

Wang, R., Depp, D., and Hall, S. J. (2005). Monolayer liposomes: synthesis and properties of liposomes containing a novel glucocorticoid. Prog. Lipid Res. 44, 463–478. doi: 10.1016/j.plipres.2005.06.008

Wei, Z., Chen, Q., and Xie, H. (2005). Liposomes for oral delivery of paclitaxel in mice. J. Control Release 109, 211–220. doi: 10.1016/j.jconrel.2005.04.002

Wei, C., and Hwang, S. (2005). Intracellular proteoliposomes for delivery of mini-proteins. J. Control Release 108, 217–227. doi: 10.1016/j.jconrel.2005.05.008

Weizman, R., and Elashoff, J. (2005). Liposomes for intracellular drug delivery: prospects and limitations. Expert. Opin. Drug Deliv. 2, 465–476. doi: 10.1517/17425247.2.3.465

Wei, J., and Lutsky, I. (2004). Methods to quantitate liposome-mediated gene transfer. Adv. Drug Del. Rev. 56, 211–230. doi: 10.1016/j.addr.2003.12.006
Warner, T. D., and Mitchell, J. A. (2008). COX-2 selectivity alone does not define the cardiovascular risks associated with non-steroidal anti-inflammatory drugs. Lancet 371, 270–273. doi: 10.1016/S0140-6736(08)60137-3

Willis, M., and Forssen, E. (1998). Ligand-targeted liposomes. Adv. Drug Deliv. Rev. 29, 249–271. doi: 10.1016/S0169-409X(97)00045-9

Woodle, M. C., Newman, M. S., and Cohen, J. A. (1994). Sterically stabilized liposomes: physical and biological properties. J. Drug Target. 2, 397–403. doi: 10.3109/10611869408996813

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 23 September 2013; paper pending published: 21 October 2013; accepted: 04 November 2013; published online: 21 November 2013.

Citation: Hua S and Wu SY (2013) The use of lipid-based nanocarriers for targeted pain therapies. Front. Pharmacol. 4:143. doi: 10.3389/fphar.2013.00143

This article was submitted to Neuropharmacology, a section of the journal Frontiers in Pharmacology.

Copyright © 2013 Hua and Wu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.