European Journal of Pharmaceutics and Biopharmaceutics 142 (2019) 179–194

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Review article

Nanomedicine for the effective and safe delivery of non-steroidal anti-inflammatory drugs: A review of preclinical research

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ARTICLE INFO

Keywords:
Drug delivery
Inflammation
Nanoparticles
Non-steroidal anti-inflammatory drugs
Preclinical studies

ABSTRACT

The toxicity of nonsteroidal anti-inflammatory drugs (NSAIDs) is one of the major limitations to their long-term use in the treatment of chronic inflammatory conditions. This review provides an overview of the preclinical efforts on the development of nanodelivery systems for NSAIDs with a focus on the effect of nanoformulation on the pharmacokinetics and pharmacodynamics of the delivered drugs. Preclinical and clinical studies have shown that nanomedicine products can reduce toxicity and enhance the efficacy of certain encapsulated therapeutics. In this context, significant effort has been devoted to the development of nanodelivery systems for NSAIDs as means in reducing their side effects. Indeed, the preclinical studies on NSAID nanoformulations have been shown to reduce the toxicity while enhancing the bioavailability of incorporated NSAIDs at equal doses compared to conventional NSAID formulations. Furthermore, compared to conventional formulations, a number of nano-formulations were able to sustain the release of the loaded NSAIDs, and improve the pharmacodynamics of the encapsulated drug in preclinical models of inflammatory diseases. These advantages have been demonstrated using various routes of administration including oral, parenteral, ocular, transdermal, and others for the nanoformulations. A review of the research results implies a great potential for the use of nanotechnology in improving the quality of life for patients taking NSAIDs for chronic conditions, through reducing drug side effects or frequency of administration. The approach may also enable the administration of higher doses of NSAID needed for off-label therapeutic indications for diseases like Alzheimer's and Parkinson's.

1. Introduction

Nanotechnology-based drug delivery systems have been researched tremendously, as means to improve the therapeutic index of different therapeutics. Most often this has been achieved through an increase in toxic drug levels rather than a decrease in drug's effective doses by the nanodelivery systems. Nanotechnology devices most often increase drug product safety, either by replacing the toxic solubilizing agents used in the conventional drug formulations, and/or by redirecting the drug from normal tissues towards the diseased site. Depending on the drug and its intended route of administration, nanodelivery systems have also been used to enhance the absorption of drugs through different biological membranes, and/or provide means for sustained drug delivery via local or systemic administration. Such properties were behind the successful translation of several nanoformulations such as Doxil®, Abraxane®, DepoCyt®, Genexol®-PM, AmBisome®, and others, from preclinical research to clinical use [1].

Non-steroidal anti-inflammatory drugs (NSAIDs) are an old class of drugs in extensive clinical use for arthritis and other inflammatory conditions. The clinical performance of NSAIDs, as anti-inflammatory, antipyretic and analgesic drugs can potentially benefit from nano-drug delivery in various ways. For instance, incorporation of an NSAID into a nanodelivery system can potentially reduce its toxicity, increase the drug's aqueous solubility and thus its dissolution and/or increase drug's permeability through biological membranes leading to faster onset of action [2]. Perhaps, the high cost and difficulty in the generation of nanotechnology-based products in large scale have limited the progress of nano-pharmaceuticals for this class of drugs (which are relatively cheaper and in chronic use) to clinic, however.

In preclinical studies, numerous nanodelivery systems have been investigated for different NSAIDs for various related disease conditions. Herein, we will provide an overview on the development of

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https://doi.org/10.1016/j.ejpb.2019.06.025
Received 4 April 2019; Received in revised form 22 May 2019; Accepted 20 June 2019
Available online 21 June 2019

Table 1
Nonsteroidal anti-inflammatory drugs classified by chemical structure and their COX isozyme selectivity.

Group/example agent	COX-2/COX-1 ratio[1]	COX selectivity[1]	Major toxicity[2]
Salicylates			
Acetyl salicylic acid (Aspirin)	3.8	More COX-1 selective	Dyspepsia, haemorrhage, GI disorders
Diflunisal	0.75	< 5 × COX-2 selective	GI disorders
Propionic acid derivatives			
Ibuprofen	2.6	More COX-1 selective	GI disorders, haemorrhage, CV risk at high doses (≥2.4 g/day)
Dexibuprofen[3]	–	–	GI disorders, CV risk at high doses (≥1.2 g/day)
Naproxen	3.0	More COX-1 selective	GI discomfort and GI disorders
Ketoprofen	6.0	More COX-1 selective	GI disorders, acute kidney injury
Flurbiprofen	51	More COX-1 selective	Haemorrhage, GI disorders
Fenoprofen	1.0	Nonselective	GI disorders
Heteroaryl acetic acids			
Aceclofenac[4]	–	–	GI disorders, CV risk
Diclofenac	0.23	< 5 × COX-2 selective	Increased risk of thrombotic events (dose 150 mg), GI disorders
Ketorolac	294	More COX-1 selective	GI disorders
Tolmetin	2.6	More COX-1 selective	GI disorders
Alkanones			
Nabumetone	–	–	GI disorder, skin reaction
Indoleacetic, Indeneacetic acids			
Etodolac	0.043	5–50 × COX-2 selective	GI disorders, CV risk
Indomethacin	4.3	More COX-1 selective	GI disorders
Sulindac sulfide	0.29	< 5 × COX-2 selective	GI disorders, heart failure
Oxicams			
Lornoxicam	–	–	GI disorders
Meloxicam	0.091	5–50 × COX-2 selective	GI disorders, risk of CV events
Piroxicam	0.47	< 5 × COX-2 selective	GI disorders, skin reactions
Tenoxicam	–	–	GI disorders, hemorrhage
Diarylheterocycles (COXIBs)			
Celecoxib	0.11	5–50 × COX-2 selective	GI disorders and CV events
Etoricoxib	–	–	CV risk similar to diclofenac
Rofecoxib	< 0.05	> 5 × COX-2 selective	CV risk, withdrawn from market
Valdecoxib	–	–	CV risk, withdrawn from market
Fenamates			
Meclofenamic acid	0.30	< 5 × COX-2 selective	uricosuric effects
Mefenamic acid	–	–	GI disorders, convulsions
Niflumic acid	1.0	Nonselective	GI disorders

[1] Data obtained from Warner et al [3]: COX-2/COX-1 ratio (William Harvey human modified whole blood assay (WHMA)) is based on micromolar concentrations require to inhibit 80% activity (IC80); COX selectivity is determined by COX-2/COX-1 ratio.
[2] Data obtained from [4] for diflunisal, tolmetin and meclofenamic acid, from [5] for lornoxicam, from [6] for niflumic acid and from [7] for the other agents. Not a comprehensive list of side effects.
[3] Dexibuprofen (S(+)-ibuprofen) is the active enantiomer of ibuprofen.
[4] Aceclofenac is an analog of diclofenac.

nanodelivery systems for NSAIDs with a focus on the effect of nanodelivery on the pharmacokinetics and pharmacodynamics of the delivered drugs in preclinical setting.

2. Merits of the nanodelivery of non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) are a chemically diverse group of agents (Table 1), which are among the most widely used medications worldwide. Their activity in controlling inflammation and pain has been demonstrated in various conditions including rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, gout, dysmenorrhea, dental pain, and headaches [8]. These agents exert their anti-inflammatory, antipyretic, and analgesic effects through blocking the activities of the cyclooxygenase (COX) enzymes, COX-1 and COX-2, at various degrees, thus inhibiting the biosynthesis of prostaglandins and prostanoids derived from arachidonic acid.

There are several ways by which nanodelivery systems can enhance the clinical performance of NSAIDs. Most NSAIDs are weak acids and are classified as Biopharmaceutics Classification System (BCS) class II drugs because of their low aqueous solubility at acidic pH, even though they show relatively high bioavailability following oral administration [9]. However, the rate of absorption of these agents greatly depends on the dissolution of drug from the dosage form, which can substantially delay the onset of analgesic effect [10]. Nanodelivery systems, by enhancing the solubility of NSAIDs, can provide a rapid rise in plasma drug concentrations and hence, can accelerate the onset of analgesia which may be desired in the management of acute episode of pain such as dental pain or pain following surgeries [11]. Moreover, by prolonging the systemic circulation of these agents and sustaining their release, nanodelivery system can enhance the efficacy and safety of these agents, by reducing fluctuation in steady-state drug levels, for chronic use such as in rheumatoid arthritis or osteoarthritis.

A major deterrent to the chronic use of most NSAIDs is the range of adverse effects that are caused by these agents including gastrointestinal (GI) as well as renal side effects in addition to an increase in the cardiovascular (CV) risks to patients. These risks and adverse events are amplified in patients with co-existing cardiovascular, cerebrovascular, gastrointestinal, or renal conditions [12]. Interestingly, the mechanism that is responsible for the anti-inflammatory effect of NSAIDs is also suggested to be responsible, at least in part, for many of these side effects. The risk of GI and CV complications is believed to be linked to the relative selectivity of the different agents to inhibit the two COX isomers (see Table 1) even though evidence to support this assertion is lacking [8,13]. Other side effects have also been reported for NSAIDs [14].

Extensive evidence suggests that the GI side effects of most acidic NSAID arise, in part, from their contact with the mucosal epithelium [15]. This local interaction can induce gastroduodenal mucosal injury which can lead to toxic effects and impair the defensive properties of the mucosa. Encapsulation of NSAIDs into nanodelivery systems can reduce their contact with the mucus layer following oral administration, thus reducing their local irritating effects on the epithelium resulting in a substantial reduction in the GI side effects [16].

In terms of reducing the systemic toxicity as well as improving the efficacy, the superiority of nano-particulate delivery systems stems from their ability to favorably alter the biodistribution of the encapsulated NSAIDs keeping them away from sites of drug toxicity, such as kidneys and heart. Thus, encapsulation of NSAIDs while does not affect their COX-1/COX-2 selectivity, it changes the *in vivo* bio-distribution of the encapsulated drug avoiding its distribution to tissues prone to NSAID side effects. Indeed, nanodelivery systems possessing the appropriate composition and particle size have been found to preferentially accumulate in tissues with inflammatory pathologies, such as rheumatoid arthritis, through the enhanced permeability and retention effect (EPR) [17–20]. This passive targeting mechanism and other active targeting strategies such as the targeting of activated macrophages expressing folate receptors that are abundantly present in the inflamed synovial membrane by folate linked nanodelivery systems have been explored to improve the therapeutic index of NSAIDs [21].

Nanodelivery systems can improve the safety of NSAIDs by providing viable means for their localized administration limiting their systemic exposure. NSAIDs have long been administered orally or parenterally even when local anti-inflammatory effect is desired. The currently available topical formulations of NSAIDs are favored over oral NSAIDs mainly because they present fewer side effects. However, there are no convincing evidence that show these topical formulations to be as effective as oral ones [23]. Nanodelivery systems particularly with the addition of penetration enhancing components and techniques may improve the dermal delivery of NSAIDs to deeper layers of the skin with minimum systemic exposure [24]. Alternatively, the formulations can provide enhanced transdermal delivery of NSAIDs with the goal of reaching the systemic circulation while prolonging the release of the loaded drug [25]. Such formulations can potentially reduce the GI side effects of NSAIDs and/or reduce the frequency of NSAID use.

Nanodelivery systems can also be designed to enhance the localized delivery of NSAIDs through parenteral administration, such as intraarticular or subcutaneous injections near the inflamed joints. Such formulations are usually designed to prolong the residence of the encapsulated NSAID at the inflamed site and control drug release, providing a sustained therapeutic activity in order to reduce the need for frequent injections [26].

Ocular administration of NSAIDs has also been widely considered, as a less toxic alternative to ocular corticosteroids, for the relief of eye inflammation and pain associated with ocular surgeries such as cataract and refractive procedures. Several formulations of NSAIDs with relatively favorable solubility profiles have been approved for these indications and others are being explored [27]. However, these formulations face several challenges including limited drug delivery to the anterior and posterior segment of the eye due to lacrimation and/or corneal barrier function that hinders drug penetration [28]. As a result, the ocular bioavailability of NSAIDs can be improved without using excipients that can cause eye irritation [29]. Nanodelivery systems can potentially encapsulate a much wider range of NSAIDs than those currently marketed for ophthalmic use, and thus expand the therapeutic choices and scope of clinical use for ocular NSAIDs.

It has always been thought that NSAIDs can be used for off-label therapeutic indications. In fact, there are reports which support disease-modifying properties of NSAIDs in spondyloarthritis [30] and potential protection against Alzheimer's disease [31]. However, the safety profile of these agents has limited the range of doses that can be considered for such indications. For example, while observational studies have found an association between NSAID use and a decreased risk in developing Alzheimer's disease, clinical trials failed to find such an association. This has been attributed, at least partly, to the low NSAID doses used [32,33]. By improving the safety profile and biodistribution of the encapsulated NSAIDs, nanodelivery systems can permit the use of higher doses of the encapsulated drugs opening the door for research for their off-label use in other disease conditions.

3. The review of pre-clinical research on the nano-delivery of NSAIDs

We identified published reports on the nanodelivery of NSAIDs through a systematic search of PubMed from inception until December 2018. Key words used in the search included (i) the different nanodelivery systems, e.g. nanoparticle, liposome, micelle, etc, (ii) the various conditions, e.g. osteoarthritis, rheumatoid arthritis, pain, inflammation, etc, (iii) and the various NSAIDs listed in Table 1. We examined the retrieved reports and included in this review those which presented preclinical research on nanocarriers of NSAIDs, where we consider nanocarriers (also nanodelivery systems or nanoformulations) to be colloidal systems in the size range of 1–500 nm. A summary of the studies and their main elements stratified by route of administration is given in Tables 2–6. As summarized in Tables 2–6, a good amount of research work on the nanodelivery of NSAIDs through parenteral (Table 2) or oral (Table 6) routes of administration can be found in the literature. In addition, improving the local or systemic delivery of NSAIDs through alternative routes has been pursued mainly through dermal and transdermal delivery (Table 3) and to a lower extent through pulmonary and intranasal routes (Table 5). Other studies considered improving the local delivery and exposure of NSAIDs to the eyes to control ocular inflammation (Table 4). Selected studies are discussed in more details in the following section and are classified based on the key intended benefit of nanotechnology products for NSAID delivery in different indications, where the benefits as reported by the authors, are critically assessed. Readers are referred to [34] for more details on the different approaches used in the encapsulation of NSAIDS and on the *in vitro* characteristics of the nanodelivery systems.

3.1. Nanodelivery for enhancing the solubility, bioavailability, or activity of NSAIDs

NSAIDs, in general, show poor water solubility and, therefore, present variable bioavailability when administered orally. Encapsulation of these agents in nanodelivery systems present an attractive option to improve their oral bioavailability and also to permit their use in liquid dosage forms for both oral and parenteral administration. Celecoxib, a diaryl substituted pyrazole and a selective inhibitor of COX-2, is a practically water insoluble NSAID (solubility of 3–7 μg/mL) [35]. Considerable inter- and intra-subject variability in the pharmacokinetics and pharmacodynamics to celecoxib have been reported with the area under the concentration-time curve (AUC) and the peak plasma levels (C_{max}) showing a variability of about 30% [36]. In an attempt to address the low water solubility and bioavailability of celecoxib, Mennini *et al* have adopted a Quality by Design approach to design a nanoformulation for celecoxib using a micelle-forming carrier, i.e. quaternary ammonium palmitoyl glycol chitosan [11]. The optimal micellar formulation (mean size $<$ 200 nm) showed about 57-fold increase in celecoxib aqueous solubility, while an *in vivo* study showed a faster (30 min vs. 120 min) and more intense analgesia in writhing test in mice compared to an aqueous suspension made from the marketed capsule celecoxib formulation (Celebrex®). With such a low solubility of celecoxib, we can picture the large volume required to dissolve 200 mg of the drug, the currently maximum recommended one-time dose of celecoxib, if solubilizing agents and excipients are to be avoided. Improving the solubility is very desirable for such a drug, and while the 57-fold increase in celecoxib solubility by the micellar formulation

Table 2
Preclinical studies on the parenteral nano-delivery of NSAIDs.

NSAID/Carrier	Indication, route	Main Composition	Physicochemical properties*	Key results	Refs.
Aceclofenac					
SLN	OA, IV	Tristearin, HSPC, chondroitin sulfate	Size: 154.2 nm; PDI: 0.4; ZP: 19.8 mV; EE: 65.4%	↑ uptake in knee joints & prolonged control of OA	[87]
Aspirin					
CD	Cervical cancer, IP	Hydrazine monohydrate	Size: 2–5.5 nm	↑ anti-inflammatory, ↓ side effects	[88]
Celecoxib					
SLN	Arthritis, IA	C888, Poloxamer 407, sucrose	Size: 257 nm; EE: 98.75%	↑ retention in inflamed joints, ↓ systemic levels	[71]
Diclofenac					
NP	INF, IV	Ionosilica (ammonium substrucre)	Size: 150 nm; ZP: 31.3	↓ lipopolysaccharides-induced inflammation	[89]
PM	INF, IV, IP	DFEE, PEO-poly(ester)s	Size: 27.9–50.3 nm; PDI: 0.21–0.49; EE: 41–82%	Improved characteristics, ↓ heart exposure	[53,54]
LIPO	INF, IV	HSPC, Chol, DCP, DLA, DLQ	Size: 135–186 nm; ZP: ~ ⁻34 -⁻47 mV; EE: ~29–35%	↑ therapeutic availability at inflamed sites, ↑ AUC	[75]
LIPO	INF, IM	PC, Chol, α-tocopherol	Size: ~39.5 nm; PDI: ~0.29;	Protection against local tissue damage	[90]
NP	IM	PLA, Epikuron 170, benzyl benzoate/ Miglyol 810	Size: 171–252 nm	↓ muscular damage caused by	[52]
LIPO	OA, IA	Phospholipon 90G, DPPE, collagen, hyaluronan	EE: 79, 87%	Prolonged control of inflammation in OA	[91]
LGS	RA, IA	DMPC, Chol, DCP	EE: 10.8%	↑ anti-inflammatory efficacy	[72]
Etoricoxib					
NP	RA, IV	Bovine serum albumin, folic acid	Size: 215.8 nm; ZP: ⁺7.8 mV; EE 72%	Targeting potential to activated macrophages	[73]
Flurbiprofen					
PN	Acute injury, IV	Span 20 & 80, Chol, sorbitol	Size: 153–283 nm; E [91] E:60–94%	SR & ↑ AUC, $t_{½}$, & MRT	[46]
LIPO	Arthritis, IV, IP	PC, DSPC, PE-PEG	Size: 168–192; ZP: ⁻24.3 mV; EE: 52–68%;	↑ AUC, $t_{1/2}$, MRT, ↓ Cl, targeting arthritic joints	[92]
DEN	Pain, INF, IV	Polyamidoamine	–	Anti-inflammation, ↑ $t_{1/2}$, MRT	[93]
Ibuprofen					
NS	INF & Pain, SC	Polysorbate-20 derivatized by glycine	Size: 122.1 nm; PDI: 0.4; ZP: ˉ40.2 mV	pH sensitive, ↑ antinociceptive & anti-inflammatory effect	[74]
NP	Pain, & INF, IV	PEG, type A gelatin	Size: ~200 nm; ZP: ⁻23.1 mV; EE: ~70%	SR, ↑ AUC & Vd, ↓ Cl	[39]
LNC	Pain, IV	Labrafac CC, Solutol HS15, Lipoıd S75-3	Size: 47–56.5 nm; PDI: 0.054–0.094; ZP: 0.46–0.97 mV; EE: 94.2–97.7%	↑ AUC, $t_{1/2}$ & MRT, anti-inflammatory effect	[94]
Indomethacin					
NE	INF, IV	DSPC, PEG-DSPE, Chol, olive oil	Size: 180–220 nm; PDI: 0.05–0.18; ZP: ⁻30 Mv	↑ anti-inflammatory effect & ↓ side effects	[95]
PM	RA & OA, SC	β-cyclodextrin-modified PCL-PEG-PCL	Size: < 40, > 100 nm EE: 39.12–63.89%	Sustained anti-inflammatory effect	[96]
NC	AD, IP	PCL, CCT, sorbitan monostearate	Size: 236 nm; PDI: 0.17; ZP: ⁻6.9 mV; EE: ~100%	Negatively modulated neuroinflammation triggered by Aβ	[79]
NC	INF (acute chronic), IP	PCL, CCT, sorbitan monostearate	Size: 240 nm; PDI: < 0.19; ZP: ⁻6.9 mV; EE: ~100%	↑ long term anti-inflammation, ↑ safety	[48]
NP, NE	OPTH INF, IP	Chitosan & TPP/lecithin, Medium chain triglyceride;	NP size: 280 nm, ZP:⁺17 mV; EE: 85%; NE size: 240–690 nm	SR to external and internal ocular tissues.	[97]
PM	RA, SC	PNIPAAm with ethyl 4-aminobenzoate as side group	LC: 12–20.6%	↑ circulation, sustained efficacy ↓ GI side effects	[98]
MS	Arthritis, IV	Soybean oil, PC, Chol, DSPE-PEG	Size: 150 nm; EE: 95%	↑ AUC, $t_{1/2}$, MRT, ↓ Cl, ↑ uptake in inflamed joints	[99]
DEN	Arthritis, IV	Polyamidoamine	–	↑ AUC, $t_{1/2}$, MRT, ↓ Cl, ↑ uptake in inflamed joints,	[100]
LIPO	RA, IP	PC, Chol, stearlyamine	Size: 50, 100 nm	SR ↑ anti-inflammatory effect	[101]
SANS	OA, IA	PLGA, Poloxamer 407, Tetronic 90R4, glucosamine	Size: 173.9 nm; PDI: 0.24; ZP: ⁻0.66	↓ knee diameter, TNF-α levels in osteoarthritis model	[102]
PM	RA, IA	PNIPAAm, ethyl glycinate	Size: ~65–360 nm	pH dependent release, ↑ circulation, ↓ GI side effects	[70]
Ketorolac					
NP	Pain, IT	Iron-oxide	Size 6.8 nm (unloaded)	Magnetic field-dependent analgesia, ↓ COX expression	[103]
Lornoxicam					
PM	RA, IP	Tetronic® 701, Synperonic® PE/P84	Sze: 169.5 nm; PDI: 0.243	↓ elevated inflammatory serum biomarkers	[47]
Meloxicam					

(*continued on next page*)

Table 2 (*continued*)

NSAID/Carrier	Indication, route	Main Composition	Physicochemical properties*	Key results	Refs.
NSus	INF, IV	Bovine serum albumin	Size: 78.67 nm; PDI: 0.133; ZP: −11.87 mV	↑$t_{½}$, MRT, & AUC, ↑drug in inflamed tissue	[104]
Piroxicam					
NP	Arthritis, IA	Eudragit RL, PLGA, PVA	Size: 221.8 nm; PDI: 0.02; ZP: $^{+}$11.5 mV; LC: 4.06%	↑ retention in the joint & ↓ systemic exposure	[105]

Abbreviations:

nanodelivery systems: CD: Carbon dots; CS: Cubosomes; DEN: Dendrimer; ES: Ethosomes; INS: Intranasal spray; LDH: Nanocarrier layered double hydroxide; LGS: Lipogelosomes; LIPO: Liposomes; LNC: Lipid nanocapsules; ME: Micro-emulsion; MMEI: Mucoadhesive microemulsion; MP: Microparticle; MS: Microspheres; NC: Nanocapsule; ND: Nanodispersion; NE: Nano-emulsion; NLC: Nanostructured lipid carrier; NP: Nanoparticle; NS: Nanosystem; Nsus: Nano-suspension; NV: Nanovesicular system; PM: Polymeric micelles; PN: Proniosomes; SANS: Self-assembling nano-system; SEDDS: Self emulsifying drug delivery system; SLN: Solid lipid nanoparticles; SNLC: Supramolecular nano-engineered lipidic carriers.

Composition: C888: Compritol® ATO 888; CCT: Capric/caprylic triglycerides; Chol: Cholesterol; CMC: Carboxymethyl cellulose; DCP: Dicetyl phosphate; C-RH 40: Cremophor RH 40; DFEE: Diclofenac ethyl ester; DLA: Ascorbyl palmitate; DLQ: Co-enzyme Q10; DMPC: Dimyristoylphosphatidylcholine; DSPC: Distearoyl phosphatidyl choline; DSPE: Distearoyl-*sn*-glycero-3-phosphocholine; HPβCD: Hydroxypropyl-β-cyclodextrin; HPC: Hydroxypropyl cellulose SSL; HSPC: Hydrogenated soya phosphatidylcholine; IPM: Isopropyl myristate; PC: Phosphatidylcholine; PCL: Poly(ε-caprolactone); PE: Phosphatidylethanolamine; PEO: Polyethylene oxide; PEG: Polyethylene glycol; PL: Phospholipion 90G; PLA: Poly lactic acid; PLGA: Polylactic glycolic acid; PNIPAAm: Poly(N-isopropylacrylamide); PVA: Polyvinyl alcohol; PVP: Polyvinylpyrrolidone; SA: Stearic acid; TPP: Sodium tripolyphosphate; TPP: Sodium tripolyphosphate; Tw80: Tween 80; VP: Vinyl pyrrolidone.

Conditions: AAU: Acute anterior uveitis; AD: Alzheimer's disease; IBD: Inflammatory bowel disease; INF: Inflammation; OA: Osteoarthritis; OPTH: Ophthalmic; PD: Parkinson's disease; RA: Rheumatoid arthritis.

Routes of Delivery: buc: Buccal; IA: Intraarticular; IM: Intramuscular; IP: Intraperitoneal; IT: Intrathecal; IV: Intravenous; SC: Subcutaneous.

Properties and other: ↑: Increased; ↓: Decreased; AUC: Area under the curve; C_{max}: Peak plasma levels; COX: Cyclooxygenase; GI: Gastrointestinal; EE: Entrapment efficiency; MRT: Mean residece time; PDI: Polydispersity index; SR: Sustained release; $t_{½}$: Half-life; ZP: Zeta potential.

marks a good progress, the volume remains large and further increase in solubility is desirable and has been attained by other nanoformulations for other agents [37].

Parekh *et al.* investigated the potential of self nanoemulsifying granules for improving the solubility of meloxicam, an oxicam NSAID with a selective COX-2 inhibitory effect, and whether this would ultimately result in a rapid onset of action [38]. The final formulation which contained a mixture of Labrafil and stearylamine (5% w/w) as the oil phase, a mixture of Cremophor RH 40 and Tween 80 (1:1 w/w) as surfactants, and Transcutol HP and PEG 400 (1:2 w/w) as co-solvents reached a meloxicam level of 26.4 mg/g of formulation. This enhancement of meloxicam content in the granule is expected to translate to improvements in the aqueous drug concentrations upon dilution in water; however, such details were lacking from the report. *In vivo* analysis showed that at a pre-emptive meloxicam dose of 1 mg/kg in a carrageenan-induced rat paw edema model, the nanoformulation provided a rapid and more intense anti-inflammatory effect resulting in ~ 26% inhibition of paw edema at one hour post carrageenan dose, which was maintained for the entire period of the experiment (5 h). This is in contrast to the free drug suspension, which resulted in a gradual and less intense effect with no noticeable inhibition of paw edema in the first hour post carrageenan dose [38].

To address the reduced exposure and rapid elimination of ibuprofen from the systemic circulation, a PEGylated gelatin-based nanoparticle formulation (mean size ~ 200 nm) of ibuprofen sodium for IV dosing was investigated [39]. Toxicity studies and histological analysis of tissues confirmed the safety of the formulation. Moreover, PK analysis in healthy rats showed that ibuprofen in the PEGylated nanoparticles had a 4.5-fold higher area under the plasma concentration versus time curve (AUC) compared to free ibuprofen with measurable plasma concentrations up to 5 days post dose. This formulation has the potential to reduce the frequency of ibuprofen administration in future clinical application, especially when IV dosing is warranted.

In general, all NSAIDs show good activity in the management of pain and inflammation at the recommended doses. However, it is still desirable to improve the activity of these agents in order to achieve the anticipated therapeutic outcomes at lower and less frequent doses, so that their dose-dependant toxic side effects can be controlled better. Several nanodelivery systems have been designed to achieve this aim. For example, a cremophor EL-based nanoemulsion formulation of aspirin, the most widely used NSAID agent in the world, resulted in a substantial inhibitory effect on carrageenan-induced paw edema model of inflammation in rats at 4 h post oral dose of 60 mg/kg, about double of the inhibitory effect achieved with an aspirin suspension at the same dose [40]. Moreover, the same formulation led to a higher inhibition of abdominal writhing, (~91% vs 81%) compared to the aspirin suspension in an acetic acid-induced writhing model of pain. The authors attribute the improvements to the properties of the nanoemulsion, in general, including that it is kinetically stable and often lead to increased drug solubility, rapid dissolution, and high bioavailability after oral administration. Although the authors did not measure the bioavailability of the drug, they used cremophor EL and transcutol in their nanoformulation, which both have been shown to enhance the bioavailability of several drugs via multiple ways e.g. by enhancing solubility, permeability, and/or inhibiting Cytochrome *P*-450 enzymes [41–43].

Nagai *et al.* reported on a solid nanoparticle formulation for oral administration of indomethacin, a derivative of indoleacetic acid. The nanoparticles (mean size ~80 nm) were composed of methylcellulose and 2-hydroxypropyl-β-cyclodextrin and prepared using bead mill method. They investigated these nanoparticles administered at two indomethacin doses, a low dose of 0.4 mg/kg and a higher therapeutic dose of 2 mg/kg, in comparison to the high dose of 2 mg/kg of a conventional indomethacin formulation, microparticles (mean size ~ 17 μm) prepared with methylcellulose and 2-hydroxypropyl -β-cyclodextrin [44]. The nanoparticles, at the low and high doses,

Table 3
Preclinical studies on dermal and transdermal nano-delivery of NSAIDs.

NSAID/Carrier	Indication	Main Composition	Physicochemical properties*	Key results	Refs.
Aceclofenac					
NP	Gout	PLGA, PVA (NP given with uricase)	Size: 288.5 nm; PDI: 0.23; ZP: ⁻30.5; EE: 85.4%	Removed urate crystals, ↓ gout inflammation	[106]
NLC gel	INF	Stearic acid, Pluronic F68, Phospholipon 90G, oleic acid	Size: 233–286 nm; ZP: ⁻9.2 -⁻13.1 mV; EE: 67–82%	Faster and prolonged anti-inflammatory activity	[107]
Aspirin					
NE	INF	Polysorbate 80, soybean oil	Size: 90 nm	↓ ear lobe thickness, ↓ auricular levels of IL-1α & TNFα	[108]
PM	INF	PEG-600 with pendant functional groups	Size: 20–50 nm; LC: 20%	↑ anti-inflammatory effect	[109]
NE	wound healing	Stratifin, CMC, medium chain triglyceride;	Size: 113–205 nm; ZP: ⁻8.1-⁺4.5	SR, ↓ scar elevation & inflammation	[110]
Celecoxib					
SLN	RA	Capmul MCM C10 Tw80, Transcutol	Size: 240 nm, PDI < 0.3; EE:~ 86%	↑ skin permeation, ↓ arthritis index	[111]
LIPO gel	OA	PC, Chol, Pluronic F127	Size: 600–1000 nm; EE: 90–97%	↑ skin permeation, ↑ anti-inflammatory effect	[112]
NE	INF	Lecithin, OA, chitosan, Pluronic F68	Size: 238,285 nm; ZP: ⁺42.2,⁻33.9 mV; EE: ~99%	↑ skin accumulation, ↓ skin permeation	[113]
NLC gel	INF	Glyceryl dilaurate, Capmul MCM, C-RH 40, Transcutol	Size: 169 nm; PDI: 0.624; EE: 35%	Faster onset, elicited prolonged activity (24 h)	[60]
ME	UVB- INF	IPM, C8/C10 mono-/di-glycerides, Carbopol 934	Size: 104–316 nm	Anti-inflammatory effect, ↑ skin permeation	[114]
Diclofenac					
ES	INF	Chol, soy phosphatidylcholine	Size: 144 nm; ZP: ⁻23 mV; EE: 71%	↑ skin permeation & ↑ anti-inflammatory effect	[115]
Diflunisal					
SNLC gel	RA	Phospholipion 90G, C888, oleic acid, Carbopol 934	Size: ~188 nm; PDI: 0.25; ZP: −12.28, EE: 87%	↑ inhibition of ear & paw oedema	[57]
SLN	Arthritis	C888, Tw80, Butanol	Size: 124 nm; PDI: 0.29; ZP:-13.6, EE: 76.8%	↑ skin permeation & retention, ↓ oedema, ↓ leukocytes	[116]
DEN	Chronic arthritis	Polyamidoamine	–	↑ skin permeation, bioavailability & antinociceptive effect	[62]
Etoricoxib					
CS	RA	Poloxamer 407, monoolein	Size: 136–288 nm; ZP: ⁻18.4-⁻36.10 mV;	↑ bioavailability, half-life, MRT (vs. oral capsules)	[84]
ME	Arthritis, INF	1-butyl-3-Methylimidazolium hexafluorophosphate, Tw80	Size: 32.44 nm; PDI: 0.21; ZP: 0.221 mV;	↓ inflammation w/o anatomical or pathological changes	[117]
Fenoprofen					
NV	Arthritis	Span 60, Tween 60	Size: 536 nm; ZP: ⁻29.8 mV; EE: 49.1%	↓ inflammation & oedema	[118]
Flurbiprofen					
NS	INF	PLGA/PLGA-PEG, HPβCD	Size: 96–234 nm; PDI: 0.048–0.12; ZP:⁻32-⁻10 mV	SR, reservoir & anti-inflammatory effect	[24]
SLN	RA, OA	Stearic acid, Chol, lecithin, butanol	Size: 640–990 nm; ZP:⁻49-⁻20; EE: 71.5–92.7%	↑ & sustained anti-inflammatory effect	[119]
Ibuprofen					
NE	Arthritis	Almond oil, Tw80, Span 80, ethanol	Size: 21–24 nm; LC: 2.5%	Improved analgesic and anti-inflammatory effect	[59]
NP gel	RA	Carbopol 934, HPβCD, methylcellulose	Size: 208 nm	↓ inflammation, ↓ side effects, ↑ permeability	[120]
NLC	OA	Witepsol E85, Miglyol 812, Lutrol F68	Size: 106 nm; LC: 9.85%; EE: 98.51%; ZP −18.4 mV	↑ skin permeation	[121]
ME	Chronic INF	Nonionic surfactants & poloxamer 407	Size: 15–17 nm	↑ antihyperalgesic effects in prophylactic treatment	[122]
LIPO	RA	PC, Chol, Carbopol® 934	Size: 159 nm; PDI: 0.33; ZP:⁻70 mV; EE: 49%	↑ skin permeation, ↑ AUC & C_{max}	[123]
ES gel	INF, fever	Buspirone HCL, Carbopol	Size: 200 nm; ZP: 7.16 mV	↑ circulation, ↑ bioavailability	[25]
Indomethacin					
NP	INF	HPC, zirconia beads, hydrophilic ointment	Size: 72 nm	↑ skin permeation, ↓ inflammation	[124]
NP gel	RA	HPβCD, methylcellulose;, Carbopol 934	Size: 173 nm	↑ anti-inflammation & localization in the skin	[125]
LIPO	INF	Chol, dipalmitoyl-L-α-phosphatidylcholine	Size: 200 nm; PDI: 0.03; EE: 84%.	Sustained anti-inflammatory effect	[85]
Ketoprofen					
NP	INF	HPC, zirconia beads, hydrophilic ointment	Size: 68 nm	↑ skin permeation, ↓ inflammation	[124]
NP gel	RA	Methylcellulose, Carbopol 934	Size: 83 nm	↑ skin penetration, ↑ Ka & AUC in skin	[126]
ME gel	INF	Clove oil, Propylene glycol, Tween 20, gelling agent	Size: 396 nm; ZP: ⁻12 mV	SR, ↑ skin permeation	[127]
DEN	Chronic arthritis	Polyamidoamine	–	↑ skin permeation, bioavailability	[62]
Lornoxicam					
SLN, NLC, NE	INF	C888, Lanette O, oleic acid	Size: 141–295 nm	↑ drug skin penetration	[128]
NE	INF	Pluronic® F68, Tween® 80, oleic acid	Size: 139 nm; PDI: 0.233; ZP: ⁻36 mV	↑ skin permeation, ↑ anti-inflammatory effect	[129]
Meloxicam					
ES	INF	Phospholipon® 90G, Carbopol® 934	Size: 142.3 nm; PDI: 0.26; EE: 78.25%	↑ skin permeation, ↑ anti-inflammatory effect	[130]

(*continued on next page*)

Table 3 (*continued*)

NSAID/Carrier	Indication	Main Composition	Physicochemical properties*	Key results	Refs.
NS	INF	Span 60, Chol	Size: 187.3 nm;	↑ skin permeation, ↑ anti-inflammatory effect	[131]
Naproxen					
ME	Pain & INF	IPM, Span 80, Labrafil M, Labrasol, Cremophor	Size: 1.4–2.8 nm; PDI: 0.37–0.48	↑ skin permeation	[132]
PM	INF	PEG-600 (& pendant groups)	Size: 20–50 nm; LC: 7%	↑ anti-inflammatory effect	[109]
Piroxicam					
NP	INF	HPC, zirconia beads, hydrophilic ointment	Size: 75 nm	↑ skin permeation, ↓ inflammation	[124]
SLN	RA, OA, trauma	Glycerol monostearate, Tw80, lecithin, Oleic Acid	Size: ~102 nm; PDI: 0.262; ZP: $^{+}$30.2 mV; EE: 87.5%	↑ skin penetration, ↑ anti-inflammatory effect	[133]
LIPO	INF	Soya PC, Chol, stearylamine	Size: 278 nm; EE: 12.73%	↑ topical anti-inflammation	[134]
Tenoxicam					
SLN Gel	RA	Precirol, poloxamer 188, lecithin	Size: 58.1 nm; EE: 69.6%	↑ anti-inflammation, ↑ skin AUC (vs. *in vitro* results)	[135]
ME	Arthritis	Captex 300, oleic acid, Tw80	Size: 106,122 nm; ZP: ≈0 mV	↑ skin permeation, ↑ anti-inflammatory effect	[58]
Valdecoxib					
NLC gel	INF	Glyceryl dilaurate, Caproyl 90, C-RH 40, Transcutol	Size: 157 nm; PDI: 0.582; EE: 51%	Faster onset, elicited prolonged activity (24 h)	[61]

Abbreviations: (See note below Table 2).

resulted in comparable indomethacin bioavailabilities that are 5.3-fold higher than that for the conventional formulation in adjuvant arthritic (AA) rats. This translated for the low dose formulation to a comparable activity in controlling paw edema resulting from AA for up to 42 days, to that achieved with the higher dose of the conventional formulation of indomethacin. Equally as important, the nanoparticles showed a significant reduction in GI lesions.

In another study, diclofenac, a phenylacetic acid derivative, was encapsulated in liposomes based on propanediol and lecithin for oral administration and its antinociceptive activity was studied in different nociceptive experimental models [45]. At an equimolar dose of 20 mg/kg, the liposomes (mean size ~ 260 nm) resulted in a potent antinociceptive activity on acetic acid-induced abdominal constriction in mice which appeared to be dose-dependent, reaching an antinociceptive effect at 79% compared to 56% for the free diclofenac. Moreover, the liposomes showed a potent pain inhibition effect in the formalin test in rats, resulting in 79% pain inhibition compared to 61% for free diclofenac. The authors suggested that the stronger peripheral mediated antinociceptive effect for the liposomal formulation compared to the free drug was attributed to the improvements in diclofenac solubility and a better delivery to the intended sites of action.

Verma *et al.* studied the PK and PD profile of a nanoformulation used for intravenous administration of flurbiprofen, a propionic acid derivative NSAID [46]. They prepared preniosomes, dehydrated formulations, based on a sorbitol, cholesterol and an optimized ratio of the non-ionic surfactants Span 80 and Span 20, that spontaneously form niosomes upon aqueous hydration. The PK study revealed that the preniosomes (mean size < 200 nm) provided higher concentrations 8 h post dose and remained in the systemic circulation for over 3 days resulting in an AUC that is 2.6-fold higher compared to a control flurbiprofen solution. At the same dose (2.5 mg/kg), control flurbiprofen was cleared from the body in 24 h. The PD study, on the other hand, showed that the preniosomes provided a superior anti-inflammatory effect as evidenced by a significantly higher inhibition of paw edema, in a carrageenan-induced edema model in rats, being observed for an extended period of time (2–24 h post-dose) compared to the control flurbiprofen solution. The maximum inhibition by the preniosomes was 88.6% at 0.16 h post-dose while the control flurbiprofen solution showed a maximum inhibition of 64% at the same time.

In another report, a nanomicellar formulations for lornoxicam, an NSAID from the oxicam group, based on commercially available tri- and tetra-block copolymers, Synperonic® PE/P84 and Tetronic® 701 were developed as a potential therapeutic option for RA [47]. In the carrageenan-induced hind-paw acute edema model in rats, the micellar formulation (mean size ~ 170 nm) at an intraperitoneal (IP) dose of 1.3 mg/kg showed higher inhibitory effect on paw edema at 3 and 4 h post induction of edema compared to a free lornoxicam at the same dose. However, it is not clear from the report if the difference was statistically significant. Moreover, the micellar formulation at a dose of 0.325 mg/kg was found to produce comparable results to diclofenac 3 mg/kg in the same model. However, the report did not include a justification on the dose chosen for diclofenac in the comparison. The micellar formulation, at the lower dose of 0.325 mg/kg/day, was also found to reduce edema for a prolonged period (28 days) in a Freund's complete adjuvant (FCA)-induced chronic arthritis model in rats, in contrary to the free drug which failed to achieve significant anti-inflammatory effects.

A different nanoformulation, developed with the same aim of improving the efficacy of an NSAID agent for the treatment of chronic inflammatory disease such as RA, is a polymeric nanocapsule formulation that encapsulated indomethacin [48]. The formulation was examined *in vivo* in several experimental models of inflammation. In the carrageenan-induced edema acute model of inflammation in rats, the nanocapsules (mean size = 240 nm) were found to be as effective as the free indomethacin. On the other hand, the nanocapsules established (a 1.6-fold and a 2.5-fold increase in activity in the sub-chronic edema

Table 4
Preclinical studies on the ocular nano-delivery of NSAIDs.

NSAID/ Carrier	Indication	Main Composition	Physicochemical properties*	Key results	Refs.
Aceclofenac					
NP	OPTH INF	Eudragit RS 100	Size: 238.9 nm; ZP: 40.3 mV; EE: 94.53	↑ inhibition of PMN migration, lid closure scores	[136]
NP	OPTH INF	Eudragit RL 100	Size: ~135 nm; PDI: 0.186; ZP: $^{+}$30.5 mV; EE: 95.73%	↑ corneal permeation, ↑ anti-inflammatory activity	[65]
Celecoxib					
SLN	OPTH INF	Glycerol monostearate, PVA	Size: 198.77 nm; ZP: $^{-}$16.2 mV; EE: 92.5%	Anti-inflammatory effect, ↑ retention on ocular surfaces	[137]
Diclofenac					
NP	OPTH INF	N-Trimethyl chitosan, TPP	Size: 155 nm; PDI: 0.2; ZP: 8.3 mV; EE:93.3%	↑ ocular bioavailability & ↓ dosing frequency	[66]
PM	OPTH INF	Methoxy PEG-PCL	Size: 54–94 nm; PDI: 0.1–0.2; ZP: 0 mV; EE: 73–77%	↑ ocular bioavailability & C_{max}	[138]
Dexibuprofen					
NS	OPTH INF	PEG, PLGA	Size: 136, 173.7 nm; PDI: 0.084–0.097; ZP:$^{-}$15.9- $^{-}$14.1	Anti-inflammatory, ↑ corneal permeation & retention	[139]
Flurbiprofen					
NP	Cataract surgery	PLGA-PEG-POD (Peptide for ocular delivery), Lutrol F68	Size: 170–220 nm; PDI: 0.06–0.09; ZP:$^{-}$ 30–30 mV	SR, ↑ anti-inflammatory effect	[67]
NP	OPTH INF	PLGA, poloxamer 188	Size: 232.8,277.6 nm; ZP: 25, $^{-}$27.5 mV; EE: 95,94%	↑ anti-inflammatory effect	[140]
NE	OPTH INF	Flurbiprofen axetil, Caster oil, Tw80, Carbopol 974	Size: ~152–238 nm; PDI: 0.20–0.26; EE: 98.1–99.2%	↑ exposure in aqueous humor, anti-inflammatory	[141]
LIPO Gel	OPTH INF	PC, dipalmitoyl phosphatidylglycerol, Chol	Size: 113.8 nm; PDI: 0.2; ZP: $^{-}$23.8 mV, EE: 2.91%	↑bioavailability & MRT in aqueous humor & retina	[63]
Ibuprofen					
NP	OPTH INF	Eudragit RS100	Size: ~100 nm; ZP: +40/+60 Mv	↑ exposure in aqueous humor, anti-inflammation	[64]
Indomethacin					
NP	OPTH INF	HPβCD, methylcellulose;	Size: 76 nm	↑ ocular bioavailability, ↑ corneal wound healing	[142]
Ketorolac					
ND	OPTH INF	Eudragit RL 100, PVA	Size: 252.8 nm; PDI: 0.51; ZP: 16.8 mV; EE: 91.6%	↑ Ocular bioavailability & residence time	[143]
PM	OPTH INF	NIPAAM, VP, acrylic acid, Bis-acrylamide	Size: 35 nm	↑ bioavailability, prolong anti-inflammatory effect	[144]
Piroxicam					
NP	AAU	Eudragit RS100, PVA	Size: 230–250; ZP: ~35 mV	↓ inflammation locally	[145]

Abbreviations: (See note below Table 2).

model and the arthritis model, both of which are induced by FCA, respectively. The nanoformulation also showed reduction in GI damage, compared to free indomethacin (around 58%, 72%, and 69% reduction in GI damage indices for duodenum, jejunum, and ileum, respectively).

3.2. Nanodelivery for improving the safety of NSAIDs

The most frequent side effects of NSAIDs are in the GI tract which can limit their long-term use. To reduce these side effects, Soehngen *et al.* developed liposomal formulations of indomethacin constructed with egg phosphatidylcholine for oral dosing [16]. The administration of indomethacin-loaded liposomes provided over 75% protection against ulceration in a 4 h acute model of ulceration in rats for a range of indomethacin doses (2–10 mg/kg) in comparison to free indomethacin dissolved in polyethylene glycol (PEG)-400. Moreover, in a 2-week chronic ulceration model in rats, over 99% protection against intestinal ulceration was observed by the liposomes in comparison with free indomethacin suspended in 1% methylcellulose in saline. This protection was achieved while maintaining comparable indomethacin blood concentration and efficacy. The authors attributed this improvement in GI safety to protection against local effects of indomethacin but did not rule out protection against systemic effects.

Table 5
Preclinical studies on pulmonary and intranasal delivery nano-delivery of NSAIDs.

NSAID/Carrier	Indication	Main Composition	Physicochemical properties*	Key results	Refs.
Ibuprofen					
MMEI	PD	Polycarbophil, Labrafil M 1944 CS, Tw80, Trans	Size: 46.73 nm; PDI 0.201,	↑ DA in the brain, improved motor function	[146]
NP	COPD & CF	PEG, PLGA	Size: 344 nm; PDI: 0.12;	Targeting of neutrophilic airway inflammation	[68]
MMEI	PD	Capmul MCM, Smix, Polycarbophil	Size: 66 nm; PDI: 0.18; ZP: $^{-}$21.4;	↑ DA in brain, ↑ TH neurons count in substantia nigra	[80]
Meloxicam					
Nano INS	Pain	PVA, sodium hyaluronate	Size: 135 nm	↑ residence time, better diffusion, ↑AUC	[69]

Abbreviations: (See note below Table 2).

Table 6
Preclinical studies on the oral or buccal nano-delivery of NSAIDs.

NSAID/ Carrier	Indication*	Main Composition	Physicochemical properties*	Key results	Refs.
Aspirin					
NE	INF	Pluronic F68 /L90, Transcutol, Cremophor	Size: 216,400 nm; ZP:-13.6 mV, EE: 76.8%	↑ anti-inflammatory & analgesic effects	[40]
Celecoxib					
SEDDS	Oral NF, buc	Labrafil M 2515, Tw80, PEG 400	Size: 116.9 & 124 nm; PDI: 0.499 & 0.591	↑ drug permeation, ↑ edema inhibition	[147]
NP	INF	PLGA	Size: 79.13 nm; PDI: 0.17; ZP: 21.37 mV; EE: 86.3%	↑ exposure, no change in electrolyte parameters	[51]
PM	Pain, INF	Quaternary-ammonium-palmitoyl-glycol-chitosan	Size: 185.8 nm; PDI: 0.145; ZP: $^{+}$42.9 mV	Faster and more prolonged pain relief	[11]
MP	Arthritis	Capmul MCM, Aerosil 380	EE: 70–91%	↑ anti-inflammatory effect, ↑ oral bioavailability	[148]
Dexibuprofen					
NS	AD	PEG, PLGA	Size: 195.4 nm	↓ memory impairment & brain inflammation	[78]
Diclofenac					
NP	INF	PLGA	Size: 221.03 nm; ZP: 20.86; EE: 76.48%	↓ renal necrosis	[50]
LIPO	Pain	Pro-lipo^{TM} duo	Size: 260.2 nm; PDI: 0.27; EE: 87.4%	↑ antinociceptive efficacy dose dependently	[45]
Ibuprofen					
LNC	Pain	Labrafac CC, Solutol HS15, Lipoıd S75-3	Size: 47–57 nm; PDI: 0.05–0.09; ZP: 0.46–0.97 mV; EE: 94.2–97.7%	↑ AUC, $t_{1/2}$ & MRT, anti-inflammatory effect	[94]
Indomethacin					
Solid NP	RA	HPβCD, methylcellulose;	Size: 76 nm	↑ bioavailability & reduce GI side effects	[44]
Redox NP	Chronic INF	MeO-PEG-b-poly(chloromethylstyrene)	Size: 39.6,46.3 nm; PDI: 0.147,0.39; EE: 100%	↑ bioavailability, ↓ side effects in small intestine	[49]
PM	RA	PNIPAAm, ethyl glycinate;	Size: ~65–360 nm	pH dependent release, ↑ circulation, ↓ GI side effects	[70]
DEN	RA	Folate-PEG-PAMAM	EE: ~55%	↑ AUC, $t_{1/2}$, MRT, ↓ GI effects, ↑ uptake in inflamed joints	[21]
LIPO	INF	PC monophasic vesicles	Size: ~500 nm	↓ or eliminated gastric and intestinal ulceration	[16]
Mefenamic acid					
LDH	Pain, INF	Magnesium, aluminum	Size: 132 nm; ZP: $^{+}$36.3 mV	Hemolysis, ↓ leucocytes, neutrophils, inflammation,	[149]
Meloxicam					
SNEG	Arthritis	Labrafil M 1944 CS, SA, Tw80, C-RH 40, PEG400	Size: 173.8 nm; PDI: 0.37; ZP: ≈0 mV	Rapid onset of anti-inflammation	[38]
NC	Pain, INF	Carbopol 940, Span 60	Size: 283 nm; ZP: $^{-}$14.5 mV	↑ prolonged anti-inflammatory effect	[150]
Mesalazine					
NP	Colitis	Silica	Size: 136 nm;	↓ inflammation, ↓ toxicity	[151]
NP	IBD	PCL	Size: 221, 330 nm; PDI: 0.12, 0.21, ZP: $^{-}$1.2,$^{-}$ 2.5 mV	↓ dose, ↓ clinical activity score & myeloperoxidase activity	[152]

Abbreviations: (See note below Table 2).
* Oral delivery unless indicated otherwise.

In addition to inhibition of the production of prostaglandin in the GI tract, NSAIDs are suggested to induce mucosal damage via the over-production of reactive oxygen species (ROS). To counter this effect, Yoshitomi *et al.* developed indomethacin loaded polymeric micelles (redox nanoparticles) based on a diblock copolymers composed of methoxy PEG as the hydrophilic shell block and a hydrophobic block consisting of poly(4-methylstyrene) possessing a side chain of nitroxide radicals as ROS scavengers [49]. The redox nanoparticles at an indomethacin dose of 30 mg/kg given orally led to higher indomethacin systemic availability resulting in an AUC that is 50% higher than that of free indomethacin. Moreover, histological assessments and measurements of oxidative stress markers in the small intestine revealed that, unlike free indomethacin or indomethacin entrapped in non-redox nanoparticles, the redox nanoparticles did not cause severe damage to the small intestine, which is believed to be due to their ability to scavenge reactive oxygen species.

In a different study, Harirforoosh *et al.* attempted to study the GI and renal safety of diclofenac encapsulated in poly(lactic-*co*-glycolic) (PLGA) nanoparticles given orally to rats at a diclofenac dose of 10 mg/kg in comparison to free diclofenac [50]. Histological assessment at 24 h post-dose revealed that, while free diclofenac resulted in higher renal necrosis compared to vehicle, the nanoparticle did not significantly affect renal necrosis. All other parameters studied which included urinary and blood electrolytes as well as duodenal and gastric prostaglandin E_2 (PGE_2) and myeloperoxidase levels did not differ between the free and encapsulated diclofenac, which could be due to the short exposure time to the NSAID. The renal protection observed with diclofenac encapsulation was not observed when the investigators encapsulated celecoxib instead [51]. Rather, encapsulation of celecoxib in PLGA nanoparticles appears to have provided a GI protection by stabilizing the reduction in PGE_2 observed with the free celecoxib solution.

Nanodelivery system can also improve the safety of parenterally administered NSAIDs by reducing the toxicity at the injection site. Guterres *et al.* investigated diclofenac loaded in PLA nanocapsules with different oily cores for intramuscular (*IM*) administration in rats by measuring plasma creatine phosphokinase (CPK) activity, which indicates muscle damage at the injection site [52]. Nanoformulations prepared with Miglyol 810 core (caprylic/capric triglyceride)

(containing 0.8 mg of diclofenac) showed significantly lower CPK activity compared to the diclofenac solution. Meanwhile, when a core of benzyl benzoate was used in the preparation of nanoformulations, no reduction in CPK activity was observed compared to diclofenac solution. Histopathological assessment 3 days after the injection confirmed a reduction in local inflammation following administration of the former nanoformulations of diclofenac.

Using the same approach, the safety of a liposomal formulation of diclofenac based on phosphatidylcholine, cholesterol, and α-tocopherol, was established [90]. Liposomal diclofenac (0.2 mg diclofenac) given *IM* to rats resulted in no change in CPK activity compared to the control untreated groups, to the contrary of free diclofenac. Histopathological assessment of muscles around the injection site performed at 3 and 7 days post-injection showed intense damages in rats that received free diclofenac, but not in those that received liposomal diclofenac.

One of the major limitations to the chronic use of NSAIDS is the increased CV risk associated with these agents. We have developed several polymeric micellar formulations for diclofenac, an NSAID that is known for its high cardiotoxicity profile, and for its more hydrophobic derivative diclofenac ethyl ester (DFEE) based on poly(ethylene oxide) (PEO) as a shell block and various poly(esters) as core blocks [53]. The optimal formulations, based on a core block of poly(ε-caprolactone) (PCL) (PEO-*b*-PCL) or on PCL with an attached pendant benzyl carboxylate group (PBCL) (PEO-*b*-PBCL) and encapsulating DFEE (with mean particle sizes of 45.1 and 37.2 nm, respectively), favorably altered the PK and biodistribution of diclofenac in healthy rats (Fig. 1) [54]. In particular, the two micellar formulations, i.e. the PEO-*b*-PCL and PEO-*b*-PBCL based, showed significantly lower diclofenac concentrations compared to free diclofenac in the heart (0.5, 0.3 and 0.8 μg/g, respectively) and in the kidneys (0.5, 0.4, and 1.5 μg/g, respectively) at 24 h post an IV dose equivalent to diclofenac 10 mg/kg. The diclofenac heart-to-blood and kidney-to-blood ratios at 6 h post-dose were 5–12-fold lower with the nanoformulations compared to free diclofenac. These results show a strong potential for both micellar formulation in the cardiac-safe delivery of diclofenac, and possibly other NSAIDs, especially when we take into consideration reports that associate the extent of toxicities of NSAIDs and other agents with the degree of accumulation of these drugs in the relevant organs [8,55].

Further assessment of the DFEE encapsulating polymeric micelles based on PEO-*b*-PCL in the AA model in rats, showed that the formulation (at a dose equivalent to diclofenac 10 mg/kg/day for 7 days) resulted in a rapid reduction in the signs and symptoms of the disease comparable to the free drug (unpublished data). Moreover, histopathological assessment showed that the micelles as well as the free drug ameliorated the inflammatory cell infiltration that was observed in the heart and kidney tissues of inflamed rats. As a measure of cardiotoxicity, on the other hand, the polymeric micelle formulation showed signs of decreased toxicity compared to the free drug as evidenced by a reduction in the ratio of cardiotoxic over cardioprotective eicosanoids of arachidonic acid, which acts as a biomarker of cardiotoxicity, in hearts and plasma of AA rats (unpublished data).

3.3. Alternative routes of administration

NSAIDs are most commonly dosed orally especially in chronic use, but other routes such as parenteral, topical and per-rectal are also applied and shown to provide comparable management of pain and inflammation [56]. The low safety profile of systemically administered NSAIDs and the demand to improve the local delivery of these agents have led to development of several nanodelivery formulations which consider alternative routes including dermal/transdermal, ocular, and pulmonary delivery as well as local parenteral delivery for drug administration.

3.3.1. Dermal and transdermal delivery

The dermal and transdermal (TD) nanodelivery of NSAIDs have received much attention due to the range of conditions that can benefit from delivery through these routes which include chronic conditions such as RA and OA. Besides, NSAID delivery by non-systemic means have attracted attention owing to a potential to reduce NSAID-induced toxicity. In one study, Kaur *et al.* incorporated diflunisal, a salicylic acid derivative, into Phospholipion 90G to form a drug-phospholipid complex which was then incorporated in a nanostructured lipid carrier (NLC) based on Compritol® and oleic acid as the solid and liquid lipids [57]. The NLC was incorporated into polyacrylic acid (Carbopol® 934) to make it suitable for topical/TD delivery. In the mouse ear edema model of acute inflammation, the NLC formulation (1 g containing 400 μg diflunisal applied locally) led to a 2.5-fold increase in percent inhibition of mice ear edema compared to a conventional diflunisal o/w cream, prepared by the researchers, given at the same dose. Moreover, in the CFA-induced chronic arthritis model in rats, a twice daily application of the NLC formulation for 10 weeks led to a 7-fold increase in percent inhibition of paw edema and a 27% reduction in the level of the pro-inflammatory cytokine TNF-α in serum and in synovial fluid compared to the conventional cream (both applied topically on paws and joints of arthritic rats).

In another study, tenoxicam, an oxicam NSAID, was loaded in two microemulsion formulations based on Captex 300/oleic acid as oil phase and investigated in several preclinical experimental models [58]. The topical application of the microemulsion formulations (droplet size = 106–122 nm) showed improved anti-inflammatory effect compared to conventional tenoxicam topical suspension and cream and comparable effect to oral tenoxicam at equivalent doses. For instance, in the carrageenan-induced edema model in rats, the microemulsion formulations equally resulted in about 3- and 10-fold increase in

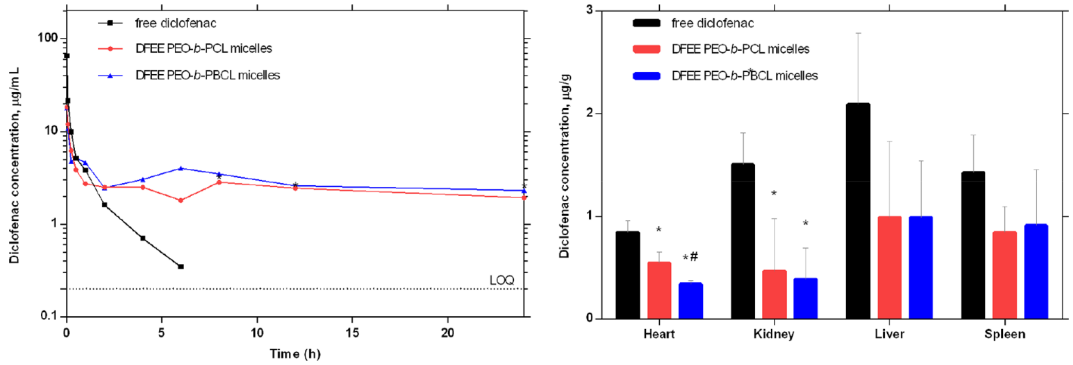

Fig. 1. Diclofenac 0–24 h blood concentration-time profile (left) and tissue distribution at 24 h (right) following the administration of DFEE loaded micelles (PEO-*b*-PCL or PEO-*b*-PBCL based) or free diclofenac (IV, equivalent to diclofenac 10 mg/kg) (Adapted from [54]). An asterisk and a hash sign indicate significantly different from free diclofenac and from PEO-b-PCL based micelles, respectively.

inhibition of edema compared the topical cream and emulsion, respectively. This was comparable to the inhibition of edema that was achieved with oral tenoxicam.

Nanodelivery systems can result in faster onset of and/or prolonged action through the TD route. For example, an ibuprofen (2.5% w/v) nanoemulsion formulation, based on almond oil as the oil phase was developed and compared to two formulations, a corresponding microemulsion also based on almond oil and a commercially available 5% ibuprofen gel (Raha Pharmaceutical Industries, Tehran, Iran) both of which had double the ibuprofen content (i.e. 5% w/v) [59]. The nanoemulsion resulted in a faster onset of anti-inflammatory effect in a carrageenan-induced rat paw oedema model, showing a decrease in inflammation in the first hour while the microemulsion and the commercial product had an onset at 2 and 3 h post-dose, respectively.

Another research group developed gels based on nanostructured lipid carriers for TD delivery of celecoxib and valdecoxib [60,61]. The celecoxib formulation based on glyceryl dilaurate as the solid lipid and capmul MCM as the oil phase was compared to a commercially available nano-sized rofecoxib TD formulation. The celecoxib nanoformulation showed a rapid onset of activity in an aerosil-induced rat paw edema resulting in about 50% inhibition of edema in the first hour compared to just over 10% for the commercial formulation. The inhibitory effect remained significantly higher at 24 h post-dose compared to the commercial formulation.

Using a different approach, Cheng *et al.* investigated the encapsulation of two different NSAIDs, diflunisal and ketoprofen, in polyamidoamine (PAMAM) dendrimers to facilitate their TD delivery [62]. PK analysis of the formulations following TD administration in rats revealed a higher plasma concentration for both drugs from the dendrimer complexes compared to free drug suspensions for the 12 h study duration. In effect, a 2.5- and 2.7-fold increase in AUC from the dendrimers compared to the free suspension for diflunisal and ketoprofen was observed, respectively. Furthermore, in an acetic acid-induced writhing model in mice, TD administration of the ketoprofen loaded dendrimers (0.1 mL of 2 mg/mL) resulted in rapid and prolonged anti-nociceptive activity lasting from 0.5 to 6 h post-dose. Whereas a ketoprofen suspension resulted in a significant activity during 4–6 h following TD administration. Meanwhile, an oral dose of ketoprofen (at a dose of 10 mg/kg) provided significant activity during 0.5–2 h post-dose. Similar results were reported for the diflunisal formulation.

3.3.2. Ocular delivery

NSAIDs have an important role in the control of pain and ocular inflammation in various conditions or following ocular surgery. In this case, local delivery to the eye is preferred, but maintaining a therapeutic concentration of the agents for an appropriate duration has proven to be a challenge. Nanoformulations can improve the ocular bioavailability of NSAIDs and increase their residence time at the desired sites.

An example is a study by Pachis *et al.* who investigated the benefits that an intravitreal injection of a hydrogel consisting of flurbiprofen entrapped in liposomes would bring to the bioavailability of flurbiprofen in the retina [63]. An *in vivo* study in pigmented rabbits revealed that this formulation had a 90% higher flurbiprofen bioavailability and 73% longer mean residence time (MRT) in the vitreous compared to a flurbiprofen solution at the same dose.

A nanoparticle formulation of ibuprofen sodium based on Eudragit RS100, a polymethacrylate-based copolymer, was found to produce rapid reductions in conjunctival inflammation and iris hyperemia induced by sodium arachidonate in rabbits [64]. The nanoformulation, administered pre-emptively 30 min prior to the induction of ocular inflammation, showed a significant reduction in inflammation that started at 30 min post inflammation-induction and was maintained up to 6 h. A comparable dose of an aqueous solution of ibuprofen lysinate showed a significant, but smaller reduction only at 2 h. This could be attributed to an increase in drug concentration in the aqueous humor associated with the nanoformulation, which at 2 h was about double of that obtained with the drug solution. Another group investigated, Eudragit RL100 nanoparticles encapsulating aceclofenac, a phenylacetic acid derivative NSAID, for ocular instillation [65]. Both Eudragit RL and SL have quaternary ammonium groups that give these copolymers positive charge. This can improve their interaction with anionic components of mucin and the cornea. The aceclofenac loaded nanoparticles showed a stronger anti-inflammatory effect as measured by higher inhibition of polymorphonuclear leukocytes migration and by lid closure scores, which dropped by 50% or more at 1–4 h post dose, in comparison to an aqueous aceclofenac solution in an arachidonic acid-induced inflammation model in rabbits.

N-trimethyl chitosan nanoparticles encapsulating diclofenac sodium [66] showed a 2.4-fold increase in time to reach maximum diclofenac concentration (T_{max}) and a 2.5-fold increase in AUC in the aqueous humor of rabbits' eyes compared to a commercial diclofenac eye drop formulation possibly due to the mucoadhesive property of the nanocarrier. The nanoparticles prolonged diclofenac residence time with therapeutic concentration being detected up to 12 h, while diclofenac from the commercial eye drops fell below detection at that time.

In a different study, Vasconcelos *et al.* considered conjugating a cell penetrating peptide ("peptide for ocular delivery" with amino acid sequence CGGG[ARKKAAKA]$_4$) to PLGA-PEG nanoparticles encapsulating flurbiprofen in order to improve their corneal epithelium penetration [67]. The formulation was examined *in vivo* in a model of ocular inflammation induced by sodium arachidonate in rabbits. Two study modes were considered, a prevention mode in which healthy eyes were treated with the formulation (or a comparator) 30 min prior to induction of ocular inflammation, and a treatment mode in which inflammation was induced first and then 30 min later the treatment was started. The nanoparticle formulation containing the peptide resulted in a better anti-inflammatory effect and showed improvements in the prevention mode, but not in the treatment mode. The investigators attributed the difference in response to a possible difference in absorption of the nanoparticles in healthy and inflamed tissues.

3.3.3. Pulmonary and intranasal administration

The nanodelivery through the intranasal (INS) or pulmonary route has been investigated for several classes of therapeutic agents including NSAIDs because of the role these delivery systems play in the local control of inflammation. An example is ibuprofen encapsulated in PEGylated PLGA nanoparticles conjugated with an anti-neutrophil antibody (NIMP-R14) for targeting neutrophils in chronic obstructive pulmonary disease (COPD) [68]. Intranasal administration of the nanoparticles was investigated in two experimental models of COPD in mice, *pseudomonas aeruginosa* lipopolysaccharide (LPS)-induced and cigarette smoke-induced inflammatory lung diseases. The nanoparticles were found to be effective in both models showing a significant decrease in the induced NFkB nuclear localization and expression as well as a decrease in the number of infiltrating neutrophils. However, the study did not compare the *in vivo* activity of this ibuprofen nanoformulation to other formulations of ibuprofen (or other indicated agents), to unloaded nanoparticles, nor to free antibody.

Using a different approach, a nanoformulation was developed for the INS administration of meloxicam. First, meloxicam particle size was reduced to the nanoscale using wet milling technology. Meloxicam particles were then incorporated into a liquid formulation with the use of sodium hyaluronate [69]. PK analysis revealed that the nanoformulation resulted in higher meloxicam plasma concentration during the first hour post-dose, which was 3-fold higher at 5- and 60-min post-dose than two equivalent formulations containing either raw or micro-sized meloxicam particles. The nanoformulation resulted in meloxicam AUC that was 3.6- and 2.3-folds higher than the equivalent dose of raw or micro-sized meloxicam particles, respectively. The authors attributed the enhanced bioavailability from the nanoformulation to

improvements in the dissolution of meloxicam due to the small particle size and also to the mucoadhesive properties of sodium hyaluronate. These results show that INS nanodelivery systems encapsulating NSAIDs not only can improve the local delivery of these agents to the lungs, but also provide an alternative route to oral dosing for their systemic delivery.

3.3.4. Parenteral administration

Parenteral administration for local delivery involves injecting the NSAIDs close to the site of action, such as the intraarticular (IA) injections at inflamed joints. These routes are favored when local anti-inflammatory effect is needed and are useful to avoid the side effects associated with full systemic delivery. With this in mind, Zhang *et al.* developed an indomethacin-loaded polymeric micellar formulation based on polyphosphazene with poly(N-isopropyl acrylamide) and ethyl glycinate as side groups [70]. A PK study in rats revealed that the subcutaneous (SC) administration of the formulation resulted in about 50% lower $C_{max,}$ but a 75% higher AUC of indomethacin compared to a free indomethacin solution (in 0.1 M Phosphate buffered saline; pH 7.4) by the same route. Anti-inflammatory effect assessment carried out in carrageenan-induced inflammation model rats, showed a significantly lower paw edema for the nanoformulation compared to the control formulations starting at 2 h post-dose. The oral suspension (5 mg/kg, PO) made from IND tablets and the free indomethacin solution (1.5 mg/kg, SC) showed significant effects at 4 h and 6 h post dose, respectively. Interestingly, a lower dose of the micellar formulation (0.5 mg/kg, SC) produced comparable or even superior activity to that achieved with the free drug given orally or as a parenteral solution. The local delivery of the nanoformulation was explored in the AA model of inflammation. All doses of the formulation (0.5, 1.5, 4.5 mg/kg) given as IA injections showed superior activity in controlling paw edema to that achieved with the free indomethacin solution (1.5 mg/kg, IA) and comparable to the oral suspension (5 mg/kg, PO) at 10- and 15-days post-AA induction. However, while the oral dosing resulted in significant gastric ulceration (as measured by number hemorrhage points, number of ulcerations, and average trauma degree), the IA administration of the micelles all doses considered, showed a substantial reduction in ulceration.

A different group encapsulated celecoxib in solid lipid nanoparticles (Compritol® 888 and poloxamer 407) with the aim of increasing its retention in the inflamed joints following IA administration [71]. A PK and biodistribution study of celecoxib and solid lipid nanoparticles, both labelled with ^{99m}Tc, after IA administration in arthritic rabbits (CFA-induced) showed that the celecoxib-loaded nanoparticles (mean size ~ 250 nm) had a significantly lower blood concentration compared to free celecoxib, which appeared to have experienced a rapid clearance from the inflamed articular joint into the systemic circulation. In a pharmacodynamic study in rats with CFA-induced arthritis, a 15-fold increase in the articular celecoxib concentrations was observed at 24 h post-dose for the nanoparticles compared to free celecoxib. The authors attribute this increase in articular celecoxib concentration from the nanoparticles to phagocytosis by the macrophages of the inflamed joints.

In another study, diclofenac sodium was encapsulated in lipogelosomes, liposomes with a polar core that is in semi-solid state of gel [72]. A biodistribution study in rabbits showed that IA administration of the nanoformulation resulted in > 4-fold increase in diclofenac concentration in the inflamed joints at 24 h post-dose compared to a free diclofenac solution. Moreover, a single dose of the nanoformulation showed an improved efficacy (over 2-fold increase) in reducing swelling of inflamed knees in rabbits (CFA-induced) compared to a commercial diclofenac product (VE-CP®, 13 mg/ml of diclofenac sodium), applied topically, containing 10-fold higher diclofenac content.

3.4. Nanoformulations for the targeted delivery NSAIDs by active mechanisms

In addition to passive targeted delivery to inflamed tissues, active targeting strategies have also been investigated in preclinical studies for the delivery of NSAIDs. One strategy is the targeting of the folate receptor, isoform FR-β, that is overexpressed in activated macrophages associated with chronic inflammatory diseases such as RA. Folate-linked imaging agents have been reported to highly accumulate in arthritic joints. In one report, folate-coupled PEG conjugates of the anionic PAMAM dendrimer encapsulating indomethacin were investigated for inflammatory tissue targeted delivery [21]. PK analysis following IP administration in AA rats revealed an increase to about 1.5-fold in AUC, 2.8-fold in $t_{½}$, and 1.8-fold in MRT for one of the folate-PEG conjugates (which contained 7 folate-PEG arms) compared to free indomethacin, and an increase to about 1.24-fold in AUC and similar $t_{½}$ and MRT compared the indomethacin PAMAM dendrimers lacking the folate conjugate. Moreover, a tissue distribution study showed that the folate-PEG conjugate resulted in 8.5-folds and 11-folds reduced uptake in the stomach in comparison to an indomethacin PAMAM dendrimers lacking the folate conjugate and free indomethacin, respectively. Less, but significant, reductions in indomethacin accumulation was also seen in the heart and kidneys, the other major sites of NSAID related toxicities.

Another folate-conjugated system investigated is a bovine serum albumin nanoparticle formulation encapsulating etoricoxib for IV administration [73]. The folate-conjugated nanoparticles significantly sustained etoricoxib release and prolonged its circulation showing an AUC that is 4.6- and 1.7- folds higher and an MRT that is 7- and 2.4-folds higher than free etoricoxib and non-targeted nanoparticles, respectively, in mice. Tissue accumulation at 24 h post-dose showed a 2.9-fold increase in etoricoxib concentration in inflamed joints compared to non-targeted nanoparticles, while the free etoricoxib fell below detection limit at the same time. The authors reported that superior anti-inflammatory effect was observed for the folate-conjugated nanoparticles in controlling inflammation in a carrageenan induced edema model when compared to both the free etoricoxib and the non-targeting nanoparticles. However, statistical data on the comparison were not found in the report.

The delivery of NSAIDs have also been investigated in pH sensitive nanodelivery systems which are designed to make use of the decrease in pH in various pathological conditions such as RA to promote release of the drug at the target tissues. In a study by Rinaldi *et al.*, ibuprofen was encapsulated in two niosomal formulations based on polysorbate-20 or its pH-sensitive derivative polysorbate-20 derivatized by glycine [74]. The two formulations were tested for nociceptive activity *in vivo* using the formalin test in mice, and the pH sensitive niosomes were found to significantly reduce licking activity at two phases of measurement, while the plain niosomes or the free ibuprofen did not show any effect. Moreover, the anti-inflammatory effect of the pH sensitive niosomes was observed in Zymosan-induced paw edema in mice where significant reduction in paw edema was observed at 1 h and maintained up to 24 h post-inflammation induction. The non-sensitive niosomes or the free ibuprofen, on the other hand, failed to show any significant effect compared to mice given the vehicle.

A different active targeting approach investigated in preclinical studies was designing nanodelivery systems with antioxidants as surface ligands to target the oxidative stress at inflamed sites. The interaction of the antioxidants with reactive oxygen species was hypothesized to enhance the retention of the loaded cargo at the inflammatory sites. To investigate this approach, Jukanti *et al.* encapsulated diclofenac in antioxidant (coenzyme Q10 and ascorbyl palmitate) modified liposomes and compared these to conventional diclofenac liposomes [75]. PK analysis in air pouch induced rats showed an air pouch fluid (APF)-to-serum drug concentration ratio that is above one for all liposomal formulations, indicating drug targeting to the APF. Liposomes

conjugated with antioxidants had larger ratios indicating superior APF targeting compared to unmodified liposomes. The therapeutic availability (i.e. ratio of dose fraction reaching target sites when a drug is administered through a nanodelivery system to that reaching the target sites when free drug is administered as IV dose [76]) was about 3-4-folds higher for antioxidant liposomal formulations compared to conventional liposomes, indicating better potential to target inflamed sites by these former formulations.

3.5. Expanding the role of NSAIDs

Inflammation plays a major role in the pathogenesis of many disease states and NSAIDs may have an expanded role in the management of such conditions, especially if combined with advanced delivery techniques. For instance, NSAIDs are believed to have a role in controlling neuroinflammation that associates various neurological diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) [77]. Properly designed nanocarrier systems can improve the permeation of NSAIDs across the blood-brain-barrier for use in such conditions. Sánchez-López *et al.* developed PEG-PLGA based nanospheres for the encapsulation of dexibuprofen, a propionic acid derivative NSAID, to increase its delivery to the brain in AD [78]. A biodistribution in mice, using rhodamine labeled nanospheres, gave evidence that at 24 h post- oral dose, the nanospheres reached the brain as well as the liver, which appears to be the elimination route of the nanospheres. However, the authors did not address the possibility of at least part of the fluorescence observed to be due to released/detached dye from the nanospheres. A behavior test performed in a mice model of familial AD (Morris water maze) using a chronic dexibuprofen treatment for 3 months (PO dose of 50 mg/kg/day; nanospheres given on alternate days) revealed that the nanospheres were more effective in spatial memory improvements compared with free dexibuprofen. Moreover, the nanospheres significantly lowered the level of β-amyloid (Aβ) plagues, a marker of AD, in transgenic mice compared to the free dexibuprofen and untreated groups. In terms of side effects, the nanospheres did not result in a significant change in gastric damage compared to the control group, while free dexibuprofen increased stomach lesions compared to both the control and the nanosphere groups.

Another group investigated the protective effects of indomethacin encapsulated in lipid core nanocapsules against the neuroinflammation induced by Aβ1-42 in an experimental rat model of AD [79]. A two-week treatment with the nanocapsules (1 mg/kg/day; IP) increased the spontaneous alteration in the Y-maze (behaviour test) and restored short (3 h following training) and long term (24 h) recognition memory, while free indomethacin failed to result in significant changes compared to the untreated group. Moreover, the nanocapsules, and not free indomethacin, blocked the decreased synaptophysin levels and suppressed glial and microglial activation. The authors hypothesized these benefits to be explained by an increase in the indomethacin concentration in brain tissue due to the advanced delivery system. This was confirmed by biodistribution study which showed the indomethacin nanocapsules to provide about 3-fold increase in cerebral indomethacin concentration compared to free drug both given at the same dose (1 mg/kg/day for two weeks). These results support a role for nanodelivery systems encapsulating NSAIDs in the management of AD.

Parkinson disease (PD) is another neurological condition that has the potential to benefit from nanodelivery of NSAIDs. Mandal *et al.* developed a mucoadhesive microemulsion encapsulating ibuprofen for INS delivery, and explored its neuroprotective effect for inflammation mediated by dopaminergic neuro-damage in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of PD in mice [80]. The microemulsion (ibuprofen 2.86 mg/kg) resulted in improvements of up to 2-folds in the motor coordination activity (in a rota-rod test) compared to the untreated group, while free ibuprofen at the same dose did not result in significant changes. Moreover, the microemulsion showed protective effect on gross neurological activity assessed through an open-field test, showing over 2-fold increase in total spontaneous activity compared to the untreated group, while free ibuprofen did not result in significant change. Moreover, the nanospheres reduced dopamine depletion and increased tyrosine hydroxylase neurons count in the substantial nigra in comparison to the untreated group.

4. Clinical research on the nano-delivery of NSAIDs

It is disconcerting, that despite the success observed in preclinical research, the translation of the developed nanodelivery formulations for NSAIDs to clinical research has been very limited and did not match the progress observed for other agents such as anti-cancer drugs or immunosuppressants [37,81]. This could be attributed to reservations of the pharmaceutical industry on the use of relatively expensive advanced delivery systems for NSAIDs that are in chronic use by patients. Difficulties in the large scale production and safety concerns as well as regulatory challenges might have contributed to the limited clinical use of nanodrug delivery in case of NSAIDs, as well [82,83]. With rapid progress in the field of nanodelivery systems such hurdles may be overcome in the near future facilitating the translation of preclinical research to clinical use of nano-NSIADs.

Among the clinical research on the TD nanodelivery of NSAIDs, cubosomal nanoparticles, nanostructured liquid crystalline particles, loaded with the selective COX-2 inhibitor etodolac were developed based on poloxamer 407 and monoolein and were clinically studied [84]. A single dose cross-over PK study in six human volunteers revealed that the TD delivery of the nanoparticles (mean droplet size = 136–288 nm) resulted in a sustained absorption, a 3.8-fold prolongation of half-life, and a 2.7-fold increase in AUC over 48 h resulting in a relative bioavailability of 266.11% compared to commercially available oral capsules (Etodolac, Apotex Corp.). However, the difference in the side effects due to the treatments, if any, was not reported. In a different study, a liposomal hydrogel of indomethacin based on dipalmitoyl-L-α-phosphatidylcholine and cholesterol (mean particle size = 200 nm) was clinically investigated as a pre-treatment topical option applied to ventral surfaces of the forearms (occluded for 6 h) of twelve healthy subjects in a UVB induced skin erythema inflammation model [85]. The percent inhibition of the UVB induced erythema, calculated from area under the erythema inhibition response-time curves, revealed that the formulation sustained the anti-inflammatory effect up to 6 h post gel removal, showing significantly improved inhibition compared to free indomethacin formulation at 3 and 6 h post gel removal. The authors attribute this benefit to a possible interaction between the lipids in the formulation and lipid structure of the stratum corneum which potentially could act as a depot for the sustained release of indomethacin.

In addition to the use of nanodelivery systems, the use of particle nanosizing technologies such as SoluMatrix Fine Particle Technology™ (iCeutica Inc., Philadelphia, PA) has been investigated for NSAIDs as a mean to reduce the doses used and consequently to reduce the associated toxicities. A review of clinical research on this approach is presented elsewhere [86].

5. Conclusion

Overall, the results of preclinical studies of NSAID-loaded nanoformulations show a great promise in enhancing the solubility, bioavailability, activity, and safety of NSAIDs. Compared to conventional formulations, a number of nanoformulations were able to sustain the release of the loaded NSAID, increase its AUC, and improve its pharmacodynamic effects in preclinical models. These positive effects have been demonstrated through different routes of administration including oral, ocular, TD, and INS. Moreover, several nanodelivery systems including liposomes and nanoparticles have demonstrated GI protection against ulceration that is usually associated with conventional formulations of non-selective NSAIDs such as indomethacin and

diclofenac. This is a very significant accomplishment not only to improve the quality of life of chronic NSAID users, but also to expand the role of these agents in the treatment of a broader spectrum of diseases. Moreover, if the toxicity of NSAIDs could be circumvented by nanomedicine, incorporation of NSAIDs into nanodelivery systems would be a valuable option for the prevention and/or treatment of diseases like AD, PD, and cancer. Taken all together, nanomedicine seems to be a promising tool for the effective and safe delivery of NSAIDs.

Acknowledgements

AL Acknowledges financial support of her research in this area by Natural Science and Engineering Research Council of Canada (NSERC), Canadian Institute of Health Research (CIHR) and Alberta Innovates Health Solutions (AIHS).

Declaration of Competing Interest

The authors have no competing interests to declare.

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