Editorial

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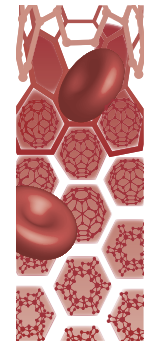
Nanomedicine



# Anti-inflammatory nanomedicines: what does the future hold?

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"researchers have focused on the design and development of a multitude of different anti-inflammatory nanomedicines"

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## Anti-inflammatory drugs

Anti-inflammatory drugs constitute the backbone of treatment for most diseases. In fact, there is a direct relationship between chronic inflammation and many emerging disorders like cancer, oral diseases, kidney diseases, fibromyalgia, GI chronic diseases or rheumatic diseases [1]. Steroidal anti-inflammatory drugs (SAIDs) and nonsteroidal anti-inflammatory drugs (NSAIDs) are key contributors in the treatment of acute inflammatory pain conditions such as headache, postoperative pain and orthopedic fractures as well as in the management of chronic inflammatory pain and inflammatory diseases like rheumatoid arthritis, osteoarthritis and gout and for ocular diseases [2]. The principal therapeutic applications of NSAIDs are related to pain, fever and they can also be used as a prophylaxis treatment after first coronary or cerebrovascular ischemic event, this is one of the most important usages of acetylsalicylic acid (ASA) [3]. Principal therapeutic areas for SAIDs are allergic rhinitis (nasally administered) [4], asthma [5], nasal polyposis and chronic rhinosinusitis [6,7]. Orally administered prednisolone, a SAID, is indicated in bronchial asthma, allergic and inflammatory disorders, rheumatoid arthritis and other collagenopathies, dermatitis and dermatoses such as subacute and chronic eczema, psoriasis and pemphigus.

## Worldwide anti-inflammatory drug consumption

Nowadays, anti-inflammatory medications are one of the most consumed type of drugs worldwide. According to the commercial source of drug utilization IQVIA [8] in 2019, ASA, diclofenac (DIC) and ibuprofen were the three main NSAIDs consumed worldwide. From September 2018 to September 2019, more than 335,000 million standard units or doses were sold. NSAIDs consumption is reported to be a bit higher than SAIDs. The leading market share of NSAIDs and SAIDs market is located in Europe and southeast Asia.

In Europe, the market is dominated by NSAIDs, with sales of ASA, DIC and ibuprofen exceeding 12,000 million standard units a year and 16,000 million in the case of ASA. SAIDs also represent a huge market in Europe, among them (in decreasing order) mometasone, beclomethasone, fluticasone and the combination of beclomethasone and formoterol.

Concerning the delivery routes of the three most consumed SAIDs worldwide mometasone, fluticasone and prednisolone, the nasal route is predominant (54.7%), followed by the oral (21.6%) and ophthalmic routes (9.9%), but it depends on the drug. These data refer to the year 2019 [8].

## Limitations of convectional anti-inflammatory therapies

Unfortunately, current anti-inflammatory therapies are unable to achieve the best conditions of efficacy and safety. It is also important to highlight that anti-inflammatory drugs lead to very expensive and serious adverse events,

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such as GI, cardiovascular and renal complications that involve health risks and can have a great economic impact. These side effects have, mainly been studied for NSAIDs [9], but side effects limit the use of SAIDs [10].

The efficacy of the anti-inflammatory therapies could be considered as the result of a delicate balance between the potency of the drug and side effects on healthy organs. Doses of these drugs are generally limited to values below the therapeutic dose, with an aim to prevent side effects. However, this often results in an insufficient amount of the active drug reaching the site of action, especially in hard to access areas such as articular cavities or different ocular structures, with a consequent loss of effectiveness. In other circumstances, administration can be severely limited by the development of tolerance, resistance or the inability of the drug to reach the biophase, and thus circulating within the whole organism.

## Nanotechnological approaches for delivering anti-inflammatory drugs

To overcome these problems, researchers have focused on the design and development of a multitude of different anti-inflammatory nanomedicines by associating these drugs with nanodelivery systems. These newly developed drug-delivery systems allow for the control of the LADME biological pathway, and can eventually improve the bioavailability of anti-inflammatory drugs. The technological characteristics of these nanomedicines will enable: the improvement of unfavorable physicochemical properties of the anti-inflammatory drugs, such as poor water solubility; the protection against inactivation chemical, enzymatic or immunological processes from the site of administration to the biophase, as well as against degradation processes that might arise during storage; the reduction of interactions with the mononuclear phagocyte system, hence prolonging circulation in the bloodstream; the facilitation of drug release at an intracellular level, allowing it to pass across different biological barriers and overcome drug resistance mechanisms; and the transport and controlled drug delivery to the biophase achieving higher dose accumulation in the inflamed area and decrease of undesirable side effects.

In relation to the prevention of the anti-inflammatory drugs, adverse events different strategies have been explored in elementary research. The use of nanoparticles as carriers of glucocorticoids showed a significant reduction of toxic effects in different studies [11,12]. Another strategy focused on the prevention of GI adverse effects is related to the use of antioxidants [13,14]. This is because there is evidence of the involvement of multiple cellular pathways in NSAIDs-mediated GI damage, related to the redox state of enterocyte. In this area, nanoparticle-based systems [15] have shown an enhanced efficacy in the suppression of NSAID-induced small intestinal inflammation by improving the accumulation of the redox molecules can be found.

## Anti-inflammatory nanomedicines in the clinic

With regard to nanotechnology-based pharmaceutical formulations there are few commercially available medicines. Nanofast® gel, a nanoemulsion containing sodium diclofenac, methyl salicylate and menthol. Oxalgin Nano® gel, also a sodium diclofenac nanoemulsion and Nanomax®, a nanoemulsion consisting of DIC, linseed oil, methylsalicylate and menthol are all nanomedical approaches that can be used for topical treatment to improve the absorption of the drug across the skin. Another product, Zilretta® consists of triamcinolone acetonide formulated into polylactic-*co*-glycolic acid microspheres. Polylactic-*co*-glycolic acid was approved by US FDA in 2017 for knee osteoarthritis treatment. Zilretta was designed for intra-articular injection delivery, despite positive results on clinical trials; it did not show better results than the immediate release formulation, a crystalline suspension of triamcinolone acetonide [16]. However, Zilretta enables a sustained release of the active drug in the synovium, providing a prolonged action, which lessens the systemic exposure and the adverse side effects related to conventional therapy.

In August 2018, the FDA approved a loteprednol etabonate ophthalmic suspension 1%, Inveltys®, which is powered by Ampplify™ a drug-delivery technology utilizing mucus-penetrating particles. These are selectively sized nanoparticles with noncovalent proprietary coatings. Loteprednol etabonate has a good potency for different inflammatory eye diseases. However, it has a low efficiency due to its rapid metabolism [17]. Therefore, Inveltys® is designed to enhance penetration through the mucus barrier and deliver an increased concentration of loteprednol etabonate to the target ocular tissue [18].

In relation to new nano-based products in clinical trials Nanocort®, a PEG-liposomal prednisolone sodium phosphate, is being testing for the treatment of rheumatoid arthritis, arteriovenous fistula, Graves' ophthalmopathy, atherosclerosis and ulcerative colitis. The most advanced trial of which is a Phase III clinical trial in rheumatoid arthritis [19]. The safety of the treatment with Nanocort® has been demonstrated previously. However, around

9.7% of patients treated with Nanocort® complained of infusion reaction and 2.7% sensed an acute infusion reaction.

It has been also reported that the use of an ophthalmic dexamethasone cyclodextrine nanoparticle suspension has optimal results [20]. In this pilot study, the nanosystem is reported to have significant efficacy against uveitic macular edema and vitritis.

Attention should also be drawn to the advances achieved in anti-inflammatory therapy by extracellular vesicles (EVs) as new drug-delivery platform for anti-inflammatory drugs [21]. EVs are nano-sized membrane derived vesicles released by almost all cell types, including exosomes, microvesicles and apoptotic bodies. These nanosystems can overcome limitations related to immunogenicity, transport, targeting and toxicity of conventional drug-delivery platforms. Several clinical trials [22] and other reported studies [23–25] have demonstrated the efficacy and safety of EVs loaded with the anti-inflammatory drugs.

Additionally, recent research has focused on the therapeutic effects in inflammatory diseases of adipose-derived mesenchymal stem cells and other biogenic nanoparticles obtained directly from lipoaspirate. They were demonstrated to offer a therapeutic alternative in the treatment of pathologies such as arthritis rheumatoid, lupus, atherosclerosis and Crohn's disease [26,27].

## Anti-inflammatory nanomedicines: a future perspective

Notwithstanding the reported advantages provided by nanotechnology and the optimistic predictions about anti-inflammatory nanomedicines made by researchers on the basis of development of different generations of nanosystems by vascular permeability, overexpression of biomarkers, immunomodulation and macrophage repolarization [28], anti-inflammatory nanomedicines have not been yet fully established commercially. In this context, only certain areas such as cancer therapeutics have been increased in the clinical translation and commercialization [29].

We, therefore, need to identify the problems in areas such as inflammation and evaluate if some of these diseases are underestimated due to their reduced mortality. While in the short term, most of these types of diseases are not fatal, they have a high impact on quality of life. Perhaps, the problem lies in the cost–effectiveness balance, which is an important issue for health systems. Equally, other crucial aspects like large-scale manufacturing, toxicity and safety, industrial property and government regulations must be analyzed in detail in comparison with currently available therapies [30].

All these dimensions override the successful results already obtained at laboratory level and hinder their clinical translation. Therefore, the future should be aimed to reconciling the technological, clinical and economic value by collaboration between regulators, industry, practitioners and academia.

### Author contributions

A Sánchez and B Clares wrote the first draft of the manuscript. AC Calpena, JL Soriano and P Gálvez contributed to the final version of the manuscript. All the authors provided critical feedback.

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