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The Potential Contribution of Nanoparticles in the Treatment of Inflammatory Diseases

Mona A. Elsayed, Ayman Norredin

Abstract

The scope of this chapter is to review the significant effect that nanomedicine has had in the treatment of inflammatory diseases. Nanotechnology has been widely studied in the last decade and proved to be an encouraging strategy in the health-care system and the medical field. This novel technology provides a vast number of nanomaterials and tools that could actually diagnose and treat different inflammatory disorders and conditions. An enormous amount of in vivo and in vitro research was conducted by many groups to validate the positive contribution that nanoparticles have in regard to the treatment of inflammation and its associated illnesses. This contribution is due to the fact that nanoparticles could be modulated to pass through metabolic barriers and specifically targeted to deliver drugs to the required sites without affecting healthy cells and tissues. This makes them a promising therapeutical choice for the treatment of inflammatory diseases in the future.

Keywords: nanoparticles, inflammation, nanomedicine, drug delivery, nanotechnology

1. Introduction

Along with the advances in drug development recently, a new technology has gained a lot of attention in the last decades; this technology is nanotechnology [1]. Pharmaceutical industries have become increasingly interested in nanomedicine, due to the huge advantages this technology provides. Nanomedicine is the application of nanotechnology to diagnose and treat biological systems in health and disease [2]. Nanomedicine has led to the development of powerful tools for biological and medical research; these developments include targeted drug delivery, implantable materials for tissue engineering, and creating nanoscale probes for medical diagnostics and tracking cell movements [3]. At times of infection or injury, inflammation plays a very important role in protecting the injured tissue from further infection by starting the healing process [4]. It does this by increasing blood flow to the damaged tissue, which increases the activity of the cells and makes the tissue appear red, hot, and swelling. So, inflammation is actually the body's own response to any damage occurred in the body, which makes it an important part of the healing process. However, if inflammation occurs by mistake, for example, in autoimmune diseases where the body attacks itself or if the inflammation stays too long, even after the infection or injury had passed, then this could

cause an inflammatory disease. Therefore, short periods of inflammation, such as with an allergic reaction or with an infection, are generally fully treatable and leave no long-term problems. On the other hand, if inflammation lasts more than several months or years, then it is particularly severe and may cause lasting damage to the affected area or organ, for example, deformed joints. Although, there are an extensive number of medications that are available for the treatment of acute and chronic inflammation in the market. However, scientists have recently started to guide their research toward nanomedicine treatments for inflammatory diseases. Many researches have been studied in vivo and in vitro regarding the treatment of inflammatory diseases with different kinds of nanoparticles. The results of most of the studies reveal a lot of promising and very successful developments. The focus of this chapter is to provide an overview in nanotechnology contribution in treating inflammatory diseases.

2. Inflammation

When a body is injured or attacked by microbial organisms such as bacteria, viruses, or fungi, the immune system is signaled for invaders by the process of inflammation. Inflammation is simply the body's mechanism of defending itself by responding to stimuli to repair and heal any signs of damaged cells or tissues. That's why inflammation is an important part of the immune system's physiological response, without which, infections and injuries could become fatal. However, if the inflammatory process is not working as it should be, it can turn into a disease. Inflammatory diseases include a massive number of disorders and conditions [4–6]. Examples include allergy, asthma, glomerulonephritis, hepatitis, and inflammatory bowel disease [5]. Chronic inflammation has been linked to certain diseases such as heart disease or stroke and may also lead to autoimmune disorders, such as rheumatoid arthritis or cancer [4].

2.1 Causes of inflammation

An infection or injury affecting the body will most probably trigger a number of physical reactions by the immune system that will eventually cause inflammation [5]. On the other hand, inflammation in any part of the body does not necessarily mean that there is a microbial infection.

The most common causes of inflammation are:

- Pathogens like viruses, bacteria, or fungi
- Injuries like external cuts or wounds
- Chemicals or radiation affecting the lungs or body

Diseases or conditions that can cause inflammation:

- Cystitis: an inflammation of the bladder
- Bronchitis: an inflammation of the bronchi in the lungs
- Otitis media: an inflammation in the middle ear
- Dermatitis: an inflammation of the skin

2.2 Kinds of inflammation

2.2.1 Acute inflammation

Acute inflammation is a short-term response with localized effects that means it works at a specific place where the problem exists. It usually occurs after an injury or wound on the skin, a sprained ankle, or a sore throat due to a bacterial infection. It starts rapidly, and symptoms are usually severe, but they subside in a couple of days or weeks. During an acute inflammation episode, the blood vessels in the area affected dilate, and therefore blood flow increases, and the white blood cells cover the injured area to promote healing. This response is what causes the injured area to turn red and become swollen [5].

2.2.2 Chronic inflammation

Chronic inflammation is a long-term response; it's mostly a persistent, low-level inflammation that can last for months or even a lifetime [7]. Inflammation begins as a defensive process in which the body is ready to protect itself from harmful pathogens or chemicals that were exposed to the body for a long period of time. However, sometimes, this defense mechanism can become uncontrolled, and hence, damage to vital organs, nervous and musculoskeletal systems, and blood vessels could occur. In some diseases the immune system might attack its own normal cells mistaking it for a foreign organism or pathogen, such as in autoimmune disorders, causing harmful inflammatory responses.

Chronic inflammatory diseases include:

- Rheumatoid arthritis, where many joints throughout the entire body are permanently inflamed
- Psoriasis, a chronic skin disease
- Inflammations of the bowel such as ulcerative colitis
- Active hepatitis

2.3 Signs and symptoms of inflammation

Signs and symptoms of inflammation can be uncomfortable, but they show that the body is trying to heal itself. They vary in severity and intensity depending whether the inflammation is acute or chronic. The most important signs that may indicate an acute inflammation are [5, 6]:

- Redness: this occurs because the capillaries in the area are filled with more blood than usual.
- Heat: this occurs because more blood flows to the affected area, and this makes it feel warm to the touch.
- Swelling: this is caused by a buildup of fluid.
- Pain: this is due to the release of chemicals during inflammation that stimulate nerve endings, making the area more sensitive to the touch.
- Immobility: there may be some loss of function in the region of the inflammation.

Not all of the signs must occur simultaneously; some might appear before the others. Some inflammations, however, could occur silently without any symptoms, especially when the inflammation is deep inside the body such as in an internal organ. The loss of function symptom, for example, is when you cannot breathe properly if you have asthma, when an inflamed arm or leg is difficult to move or when the sense of smell is lost during a nasal allergy. Inflammation does not necessarily start exactly when a person has been infected by a virus or bacteria, but it actually begins when the body starts to fight against the harmful stimulus or the infection.

Symptoms of chronic inflammation present in a different way [5, 7]. These can include:

- Constant fatigue
- Mouth sores
- Joint, chest, or abdominal pain
- Rash
- Fever

When people have inflammation, they will feel pain, discomfort, distress, and stiffness in the inflamed area, depending on the severity of the inflammation; the type of pain varies. Although inflammation, in most cases, does indicate that the immune system is working properly, the symptoms are still an unpleasant feeling and usually need treatment to ease the pain.

2.4 Treatments of inflammation

The treatment of inflammatory disorders must rely on targets present in the diseased tissues [8]. To achieve the desired therapeutic effect on inflammatory cells, high drug doses will be required which sometime can induce unwanted effects on healthy tissues. The main anti-inflammatory drugs are either steroidal such as betamethasone, prednisone, and dexamethasone or nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, and naproxen [4]. NSAIDs are available in low doses over the counter mostly to treat the pain associated with inflammation, while higher doses of NSAIDs and steroidal medication are available as prescription medications [5]. Both are used to treat acute and chronic inflammatory diseases. However, their prolonged use is associated with a lot of side effects. Steroidal drugs can cause adrenal atrophy, fluid retention, thinning of bones which can lead to osteoporosis, and increased risk of infection or injury. NSAIDs can cause peptic ulcers, allergies, high blood pressure, or liver and kidney problems. Thus, the search for new anti-inflammatory agents is getting popular with the objective to obtain greater safety, better efficacy, and a more economical way to treat inflammation [5].

Nanomedicine has grown rapidly due to the need for improved therapies for inflammatory, developmental, infectious, and degenerative nervous system disorders [9]. These disorders are a significant burden due to the increased number of people affected, disease severity, and financial cost. Therefore, the need for an improved diagnosis and treatment is urgent. Nanotechnology has been widely studied in the last decade and proved to be an encouraging strategy in the health-care system and the medical field. This novel technology provides a vast number

of nanomaterials and tools that could actually diagnose and treat different inflammatory disorders and conditions. This chapter focuses on the current and future potential of nanomedicine to positively treat inflammatory disorders.

3. Nanotechnology

The last decade has been a tremendous growth for nanotechnology; it encompasses different scientific disciplines. This field aims at designing materials with new functions and beneficial properties at the nanometer level [10]. The nanomaterials designed are mostly any shape with a size in the range of 1–100 nm [11]. The huge and unique advantages that nanoparticles (NPs) offer made them an important research in the medical field, which created a new field called nanomedicine [12]. They can be used for the prevention, diagnosis, and treatment of many diseases, due to their very small size and large surface area. In addition to their easy preparation, NPs can be used to encapsulate and protect drugs, genes, or proteins in which they are carrying from degradation, thus, enhancing their biodistribution and allowing sustained release [13]. They also improve the bioavailability of hydrophobic molecules and can be modulated for site-specific targeting, hence, decreasing the side effects of drugs. Moreover, their unique ability to pass through the physiological barriers and intercellular spaces through different mechanisms due to their small size is an important property in the treatment of different kinds of diseases such as brain disorders [13]. In many cases nowadays, current treatments are simply inadequate to decrease disease progression or even remove symptoms and signs of inflammation [9]. However, nanoparticles can solve such problems, for example, increasing drug penetration into sites of active microbial infection while decreasing its side effects by working as drug carriers. In recent years, the goal for nanoparticle development was for the treatment, detection, and prevention of inflammatory and infected sites [14–16].

Different types of nanocarriers are available, and they are fabricated and chosen depending on different aspects such as the kind of application, what is carried by the nanoparticles whether it's a drug or gene, way of administration, materials used, and method of fabrication. Types of nanoparticles include, but not limited to, polymeric nanoparticles, solid lipid nanoparticles (SLNs), liposomes, metallic nanoparticles, and dendrimers [1]. Below are the different types of nanoparticles that are mostly used.

3.1 Polymeric nanoparticles

Polymeric nanoparticles are made from natural or artificial biodegradable and biocompatible polymers; they represent a promising formulation for drug delivery [17]. They work as carriers to control drug release and target specific locations. When compared to conventional formulations, polymeric nanoparticles can increase the solubility of the drug, hence, increasing its absorption and reducing the therapeutic dose. Furthermore, these nanoparticles are stable and safe. Polymeric nanoparticles can be fabricated using various methods of synthesis, according to their intended application. They can be designed as nanocapsules or nanospheres and range from 10 to 1000 nm in diameter, differing in their composition and structural organization [1]. A nanocapsule has a polymeric membrane surrounding an oily core in which the active ingredient can be adsorbed to the membrane and/or dissolved in the oily core. Nanospheres, on the other hand, are made only from a polymeric structure, where the active constituent is adsorbed or retained. Polymeric materials that have been used extensively for nanoparticles include polylactic-acid (PLA) and poly-lactic-co-glycolic acid (PLGA) [1, 18].

3.2 Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are colloidal carrier systems that contain highly purified triglycerides, composed mainly of lipids. These structures are produced from solid lipids and are stabilized by surfactants. They combine the advantages of other colloidal systems such as liposomes and polymeric nanoparticles, in their biodegradability, biocompatibility, and low toxicity [19]. SLNs can be produced on a large scale; they have high physicochemical stability and offer good protection against drug degradation [1, 19]. Their size ranges from 50 to 1000 nm and may be used in the pharmaceutical field for the delivery of drugs using different routes of administration such as oral and parenteral routes [1].

3.3 Liposomes

Liposomes for drug delivery are spherical small-sized vesicles composed of natural or synthetic lipid bilayers, separated by an aqueous medium in their core [1, 2, 17]. Hydrophilic substances are encapsulated inside the aqueous compartment, while lipophilic substances are adsorbed or incorporated in the lipid bilayers. Liposomes are classified according to their surface charge, size, lipid composition, and method of preparation. The surface charge could be anionic, cationic, or neutral. According to the size and number of lamellae, liposomes can be classified as small, large, or giant and oligo-, uni- or multi-lamellar, respectively [1]. Liposomes have helped decrease the side effects of different drugs such as anticancer and antifungal drugs, simultaneously with improving their efficacy [2]. Liposomal drug delivery preparations have also been studied in various chronic inflammatory diseases. This is a promising approach since it limits the side effects of anti-inflammatory drugs on healthy tissues [2].

3.4 Metallic nanoparticles

Metallic nanoparticles comprise a class of materials that are made from metals such as titanium, gold, and platinum. They exhibit remarkable optical and electronic properties, which make them very useful in the medical field [20]. These nanoparticles are ranged in size from 1 to 100 nm, and they can be fabricated and modulated with several functional groups, due to their high surface area to volume ratio that allows them to be conjugated with antibodies, ligands, and vehicles for gene drug delivery and diagnostic imaging [17, 19, 21]. Moreover, metallic nanoparticles have the potential to carry large doses of drugs and increase their circulatory half-life [19]. Examples of metallic nanoparticles used in research nowadays include but are not limited to gold, silver, zinc oxide, and iron nanoparticles.

3.5 Dendrimers

Dendrimers, one of the most interesting classes of nanoparticles, are synthetic polymers with repetitively branched molecules ranging in size from 1 to 100 nm [22]. Dendrimers are radially symmetrical molecules with well-defined and homogeneous structure consisting of treelike branches [23]. A typical dendrimer is composed of different parts; it is composed of a central core surrounded by repeated units that start from the inside and grow outward like branches with multiple peripheral functional groups [24]. The functional groups have a high degree of molecular uniformity and could be adjusted in size, valency, solubility, and biodegradation [17]. The dendrimers have very high stability and huge surface area, which made them gain a lot of interest and have a wide number of applications in the biomedical field.

4. Contribution of nanoparticles in inflammatory diseases

Pharmacists, physicians, and patients have long desired better pharmaceutical formulations to improve drug efficacy, reduce toxicity, and reduce the costs of preparation and treatment [2]. The conventional treatments available for inflammatory diseases involve nontargeted treatment options with extensive adverse effects. However, nanodrug delivery has shown, in many studies over the years, a numerous number of promising approaches for delivery of therapeutic agents, and most of them proved to reduce side effects and toxicity, increase a drug's bioavailability and effectiveness at the site, and reduce cost. The focus of this section is to highlight the contribution of several nanoparticle applications that have made an immediate major impact in the treatment of different inflammatory disorders.

4.1 Rheumatoid arthritis

Rheumatoid arthritis (RA) is the most common inflammatory disease and is the major cause of disability of the joints [13, 17, 25]. This disease is associated with progressive disability, systemic complications, and socioeconomic costs [13, 17]. To deliver drugs to the target site directly is still a major problem nowadays. Thus, bounding drugs to carriers, like nanoparticles, can make cell-specific targeting become more achievable. The drugs available conventionally for the treatment of RA include three main groups; these are disease-modifying antirheumatic drugs (DMARDs), steroids, and anti-inflammatory drugs such as NSAIDs. Discussed below are examples for the contribution of nanoparticles to each group.

In one study scientists explored the use of multifunctional nanoparticles in the treatment of RA that involves small synovial joints. This study used near-infrared (NIR) light technology along with the nanoparticles [25]. In this study methotrexate (MTX), which is a DMARD, was loaded to a PLGA polymer-gold (Au) half shell nanoparticle. Then arginine-glycine-aspartic acid (RGD) peptide was conjugated to the surface of the Au NP forming a multifunctional NP (RGD-MTX-PLGA-Au). The RGD peptide was used as a targeting moiety for inflammation, the Au half shell was used to generate heat, and MTX was used for the treatment of RA. The NPs were injected into collagen-induced arthritic (CIA) mice. They were effectively delivered and accumulated in the inflamed joints due to RGD peptides. After delivery, heat was generated upon NIR exposure due to Au, and the MTX was then rapidly released from PLGA nanoparticles. The application of this multifactorial NP in CIA mice had better therapeutic efficacy with a much smaller dose of MTX, when compared to conventional treatment [25]. These results demonstrate that the targeted NPs treatment is a useful and effective strategy for increasing the therapeutic efficacy and decreasing side effects of drugs used in the treatment of RA.

Steroids have been used for the treatment of chronic inflammatory disorders for decades [26]. Normally, to reach efficacious concentrations in the blood, they are frequently injected in high doses due to their rapid clearance from the body. However, the chronic use of corticosteroids is associated with severe side effects such as osteoporosis, hypertension, and weight gain. Therefore, current corticosteroids should have active targeting, controlled release and retention in the inflamed tissue. This could be done using engineered nanomaterials as delivery vehicles. In one study, glucocorticoids were loaded into liposomes to prolong the drug circulation time and change drug distribution. As a consequence, number of injections and doses were reduced while still achieving similar efficacy to that of free glucocorticoid in rat models of rheumatoid arthritis [26].

Nano-carriers that were also successful in delivering anti-inflammatory drugs were PAMAM dendrimers [17, 26]. In one study, they have been used to deliver

indomethacin to reduce inflammation in the rat model of arthritis. The polyethylene glycol (PEG) dendrimers were functionalized with folate as a targeting ligand to target only activated macrophages, since folate receptor is expressed on activated macrophages only and not on resting ones. This folate-PEG-PAMAM dendrimer was loaded with indomethacin to study its anti-inflammatory effect. This conjugation resulted in a 10–20-fold increase in drug loading efficiency and was found to release indomethacin in the joints in a sustained manner [17].

4.2 Dermatitis

Dermatologic therapy is mainly aimed to prevent or decrease inflammation in the skin. Topical corticosteroids are the keystone of dermatologic therapy and have been used for various inflammatory conditions for their treatment or prevention [11]. Corticosteroids are often prescribed, though their use can carry significant side effects, as mentioned earlier.

In several studies, SLN corticosteroid formulations showed increased penetration compared to its traditional counterparts, resulting in penetration beyond the epidermis and into the dermis [11]. Moreover, SLN provide the added benefit of sustained release, which is a desirable feature for controlling concentration of drug in tissue over time; these properties may improve side effect profiles and dosing schedules of drugs.

NSAIDs are another main drug used in the treatment of inflammatory diseases because of their excellent anti-inflammatory and analgesic actions [10]. However, NSAIDs are associated with serious adverse effects. Therefore, whenever possible, drugs are used topically for dealing with local inflammatory diseases. Topical ointments that contain NSAIDs nanoparticles were studied for skin penetration, safety, and anti-inflammatory effects in animal models of acute and chronic inflammation. In one study, two ointments, one with normal NSAIDs and the other containing NSAIDs in nanoform, were compared [10]. Following the application of both, the study revealed that NSAID in the nanoform had increased penetration of the drug into the skin compared with the normal NSAID, suggesting a higher local activity of NSAID nanoform when applied to the skin. In chronic inflammation model, both formulations decreased foot swelling in a time-dependent manner. However, the healing rate at 7 days of post treatment was significantly higher following treatment with NSAID nanoform compared with the normal NSAID [10]. Moreover, the concentration of NSAID nanoform was much lower than those required of the normal NSAID. Hence, the potency of the nanoformulations is much higher than normal treatment [10]. NSAID nanoformulations are expected to be the basis for new dermatological products, due to their effective treatment and low side effects.

Another major dermatological product that is used by many consumers is sunscreen. Sunscreens are important tools for skincare and the first line of choice for the prevention of inflammation caused by ultraviolet (UV) rays. UV filters are crucial for the prevention of sunburn and UV-induced mutations that may lead to skin cancer. Inorganic UV filters such as titanium oxide (TiO₂) and zinc oxide (ZnO) have been used in sunscreen formulations for a long time, and they are effective in protecting against both UVA and UVB rays. Despite that, TiO₂ and ZnO filters leave an opaque white residue on the skin, which limits its use by many customers [11]. However, by reducing TiO₂ and ZnO sizes to the nanoscale, the production of translucent products is possible rather than the white coarse raw material. It has been shown that sunscreens using particles between 40 and 60 nm are capable of providing good transparency without weakening UVA and UVB protection [27]. Although there has been some concern about the use of nanomaterials in sunscreens, there is no indication that the use of TiO₂ or ZnO holds any

danger, and studies showed that nanoparticle preparations do not penetrate past the stratum corneum [28]. Therefore, further study is still needed to fully evaluate the safety of these filters and fully prove their safety.

4.3 Asthma

Asthma is a chronic inflammatory condition characterized by narrowing and swelling of the airways with extra production of mucus, which makes it difficult for the person to breathe [29]. Theophylline is a drug that had been used conventionally worldwide for the treatment of allergic asthma for several years [30]. Although it's still widely prescribed, its use has decreased due to the use of inhaled glucocorticoids instead. Moreover, theophylline has severe side effects due to its low therapeutic window, such as nausea, headache, and cardiac arrhythmias, which limits its use. The adsorption of theophylline to chitosan nanoparticles, modified by the addition of thiol groups, was studied in vivo using mouse models of allergic asthma [29].

Chitosan is a polymer derived from chitin that has been used for nanodrug delivery due to its beneficial properties such as biocompatibility, biodegradability, and bio-adhesiveness [31]. The mice were treated intranasally with theophylline alone, chitosan nanoparticles alone, or theophylline adsorbed to chitosan nanoparticles [29]. The effects of theophylline on cellular infiltration, histopathology of lung sections, and apoptosis of lung cells were investigated to determine the effectiveness of theophylline chitosan NPs as a drug-delivery vehicle for theophylline. Intranasal delivery of theophylline conjugated nanoparticles augmented the anti-inflammatory effects of the drug compared to theophylline administered alone [29]. Thus, the clinical effects of theophylline in treating asthma could be enhanced through the use of nanodrug delivery system. Nasal drug delivery is indeed a promising technique because of the large surface area in the nose, high blood flow, avoidance of first-pass metabolism, and the quick onset of pharmacological activity. Furthermore, it is reasonable to point out that the bioavailability, adsorption, and residence time of drugs administered through the nasal route would be increased using drug delivery carriers such as nanoparticles [32].

4.4 Inflammatory bowel disease

Ulcerative colitis (UC) and Crohn's disease (CD) are the two major types of inflammatory bowel disease (IBD). IBD is a chronic but relapsing inflammatory disorder of the gastrointestinal tract [33]. UC is characterized by inflammation that is limited to the colon, while CD involves any part of the gastrointestinal tract. Abdominal pain, diarrhea, and rectal bleeding are frequent symptoms in patients suffering from IBD [33]. For years, the conventional treatment of IBD consisted of anti-inflammatory medications, such as corticosteroids, aminosalicylates, and immune suppressants. However, these drugs have several side effects due to their unspecific targeting upon administration. A promising strategy toward IBD treatment would be to selectively target the inflamed colonic tissue in order to decrease side effects and increase therapeutic efficacy of the drug administered.

In one study they used mesalamine, an anti-inflammatory medication used conventionally to treat UC, in a nanoparticle formulation [34]. Free mesalamine undergoes rapid and almost complete systemic absorption from the intestine, which causes side effects and drug loss, lowering the therapeutic effect of the medication. The drug then undergoes extensive metabolism. Therefore, it is important to deliver mesalamine (5ASA) locally to the colon, in order to reduce the systemic drug absorption and thus slow down the metabolism. The drug

was covalently bound to a NP matrix polymer. Experiments in mice with colon inflammation showed a distinct retention of the mesalamine inside the NP matrix, which allowed efficient colonic targeting and slowed down the release of the drug. This approach elevated the selectivity of the drug toward the inflammation site by decreasing the rapid drug release in the proximal intestine after oral administration [34].

Nano-drug delivery represents a promising approach in inflammatory disorders, mostly due to their accumulation in the inflamed regions [33]. In another study, the drug release was triggered by the sensitivity of polymer to pH during gastrointestinal (GI) transit. Scientists combined PLGA nanoparticles with pH-triggered polymer, to provide both specific accumulation in inflamed tissue and selective drug release in the colon [33]. They used curcumin (C) as the drug of choice to treat IBD, which is known for decades for its anti-inflammatory, antioxidant, antimicrobial, anticarcinogenic, and hepato-protective effects. Anti-inflammatory effects of C have been studied in several diseases before, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and cerebral injury [35]. However, we must note that raw C is known for its poor solubility and thus low bioavailability. Moreover, it has a high rate of metabolism and rapid elimination. Thus, an IBD-specific delivery system is needed to protect C from fast degradation. This study aimed to evaluate the effects of C loaded in polymeric pH-sensitive nanoparticles in the treatment of IBD. They were also compared to a C suspension to assess the selectivity and specific delivery of C to the colon. The negative charge of the surface of nanoparticles attracted them to positively charged ulcerated tissues [36]. Hence, C-NPs exhibited suitable physicochemical characteristics, due to their small size and opposite surface charge, for colonic delivery. In vitro studies reported that encapsulated C was found to cross through the epithelial barrier better than C suspension [33].

4.5 Alzheimer's disease

AD is a type of chronic low-level inflammation that mainly affects the elderly [37]. It's considered as a progressive and devastating neurodegenerative disorder that is characterized by cognitive deterioration and decline in the quality of the patient's life [38]. An enormous amount of in vivo and in vitro research was conducted by many groups to study the effect of NPs on the treatment of AD. The following are some examples of nanomaterials that are intended to target the brain and treat AD:

Albumin NPs loaded with tacrine, which was an AD medication previously, was synthesized and administered through the intranasal route of sheep to avoid the first-pass metabolism of the drug and deliver it rapidly to the brain. Due to the small size and large surface area of albumin NPs, the delivery of tacrine was improved through the mucosa to the brain. This research was tested on sheep nasal mucosa in permeation cell [39].

Dendrimers, as mentioned earlier, are globular macromolecular structures with a densely packed surface. It was found that dendrimers could block the aggregation of Amyloid β ($A\beta$), which is one of the causes of AD. This is by binding to the protofibrils and fibrils, therefore preventing the cytotoxic effect of $A\beta$ plaques. In one study it was suggested that conjugated and unconjugated dendrimers had the ability to separate $A\beta$ deposits in vitro [40].

Gold (Au) NPs were designed to dissolve the $A\beta$ aggregates by the use of local thermal energy at a molecular level and preventing further aggregation. When Au NPs attach to $A\beta$ aggregates and a weak microwave field is applied, they produce thermal energy which dissolve the aggregation and prevent them from reforming.

Au NPs are known to have the advantage of large surface area, biocompatibility, and small size which make them very suitable in this application [41].

Polymeric NPs such as PLGA have great biocompatibility and biodegradability properties. They have the ability to encapsulate different kind of drugs and transport them to the brain by surface modification. For example, curcumin has been encapsulated by PLGA in several studies. This formulation was found to be a potential candidate for the treatment of AD due to the great properties of curcumin as mentioned earlier. Curcumin was found to bind to the A β plaques and disaggregating them, due to its anti-amyloid property, which makes this C-NP formulation a very promising drug in the treatment of AD [41].

5. Future directions

Anti-inflammatory effects of engineered nanomaterials can be intentionally achieved. This is by modulating the nanoparticle physicochemical properties and by using nanoparticles as carriers for anti-inflammatory agents. However, structure activity relationship (SAR) studies are needed to further improve this area of nanotechnology. Despite the huge amount of benefits that nanoparticle holds as drug carriers, there are still some disadvantages [13]. For example, NPs might generate toxicity due to their small size, which widen the biodistribution of the drug in the body. Hence, increasing the drugs' potency, which although beneficial, also might affect the immune response of the body and trigger toxicity. Moreover, clinical researchers have mentioned some negative factors, such as high cost and the difficulty of scaling-up processes [1]. Therefore, future nanodrug delivery studies are recommended, and these studies should focus on toxicity and on identifying key elements like dose, route of administration, physicochemical properties, and composition that might provoke toxicity. Understanding what makes the same nanoparticle beneficial in one model and toxic in another model is critical. This will aid drug delivery formulation scientists in choosing appropriate nanoparticle carriers and will clearly enhance the rapidly growing field of nanodrug delivery.

6. Conclusion

Most drugs available nowadays are limited by their poor solubility, number of side effects, frequent dosing, and nonspecific delivery. Therefore, scientists have shifted their research to using nanoparticles for the delivery of drugs to avoid those limitations. NPs are now studied to deliver two or more drugs simultaneously for combination therapy, aiming to decrease frequency of dosing and number of medications a patient is receiving and thus increasing compliance. The main advantage of using NPs is that they could be modulated and specifically targeted to match the need. Therefore, the production of nanomaterials as drug delivery carriers can offer new opportunities to provide more focused and precise treatment of inflammatory diseases and improve the potential therapeutic effectiveness of available medications [17]. We covered in this chapter the advantages of nanotechnology in the medical field and the different kinds of NPs available. We also mentioned different kinds of inflammatory diseases such as arthritis, asthma, and Alzheimer's disease and how nanoparticles were able to positively contribute in their treatment. Despite the many technical, regulatory, and legal challenges, the development of these technologies on a large scale would face, there is no doubt that there is enough desire to overcome these challenges to improve the quality of life and benefit the society [2].

Abbreviations

AD	Alzheimer’s disease
Aβ	amyloid β
CD	Crohn’s disease
CIA	collagen-induced arthritis
C	curcumin
DMARDs	disease-modifying antirheumatic drugs
IBD	inflammatory bowel disease
5ASA	mesalamine
MTX	methotrexate
NPs	nanoparticles
NIR	near-infrared radiation
NSAIDs	nonsteroidal anti-inflammatory drugs
PLA	poly-lactic-acid
PLGA	poly-lactic-co-glycolic-acid
PEG	polyethylene glycol
RA	rheumatoid arthritis
SAR	structure activity relationship
SLN	solid lipid nanoparticles
TiO ₂	titanium oxide
UC	ulcerative colitis
UV	ultraviolet
ZnO	zinc oxide

Author details

Mona A. Elsayed^{1*}, Ayman Norredin²

1 Department of Nephrology and Hypertension, University of California, Irvine, USA

2 Department of Pharmaceutical Sciences, Sharjah University, Sharjah, UAE

*Address all correspondence to: dr.mona.atta@gmail.com

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