Nanocarrier based drug delivery in inflammatory and Parkinson's Disease: A Review

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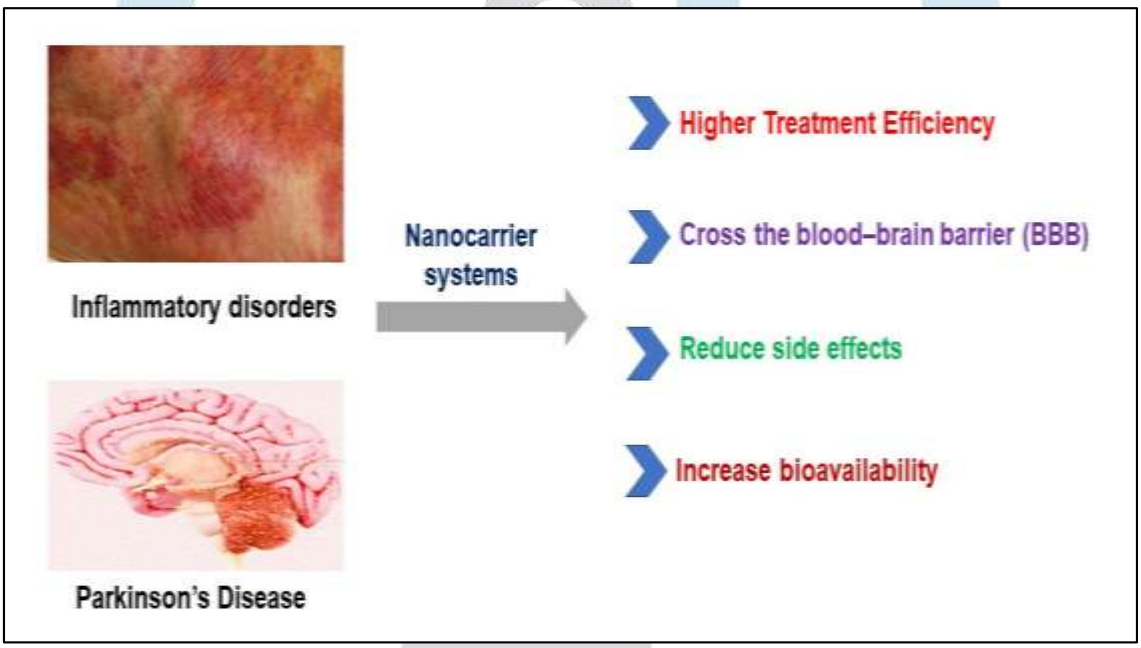
Graphical Abstract



Abstract

Inflammatory and neurodegenerative disorders, such as Parkinson's disease, affect millions of people worldwide and pose a major risk to public health. About 5 million people worldwide are impacted by it, and by 2030. To treat inflammatory diseases, rheumatoid arthritis, and degenerative diseases, numerous drugs and therapies have been developed; however, these have frequently been associated with side effects, such as drug resistance, poor solubility, decreased bioavailability, and inability to cross the blood–brain barrier (BBB). Nano carrier systems are emerging as a promising therapy option for neuroinflammatory and neurodegenerative disorders, which pose a severe threat to public health due to neuronal loss and impaired brain function. Nanocarrier systems are an excellent option for treating a variety of inflammatory and neurological disorders because of their many benefits. Furthermore, they lessen adverse effects by facilitating the precise administration of drugs to specific CNS tissues or cells. We have summarised the conventional treatment method for inflammatory and neurodegenerative disorders. We have also discussed the potential benefits of nanocarrier systems with current patented worked involved in

field of nanocarrier based drug delivery. This work helps researcher for implementation of effective treatment strategy for developing better treatment options inflammatory and neurological disorders.

Keywords: Inflammatory; Neurodegenerative diseases; Treatment; Nanocarrier system; Patents.

Introduction

With millions of victims globally, inflammatory and neurodegenerative diseases represent a serious threat to global health(1). The progressive loss of neurons along with deteriorating motor control, behavior, and cognitive function are the hallmarks of these crippling illnesses(2). Degenerative diseases arise from the breakdown of cells and tissues as a person ages, which might be caused by an unhealthy lifestyle or natural senescence(3). Parkinson's Disease affects approximately 5 million individuals globally, and by 2030, the prevalence and incidence of the disease are envisioned to escalate by more than 30% if no effectual therapies are developed(4, 5). The central nervous system and cardiovascular system are probably greatly impacted by the degenerative condition. Several drugs and treatments have been developed to treat degenerative disorders; however, these have typically been associated with side effects such as poor solubility, decreased bioavailability, drug resistance, and inability to pass the blood–brain barrier (BBB)(6).

Therefore, traditional therapeutic methods must be used to combat it; in this regard, nanotechnology has attracted a lot of attention recently. Furthermore, due to their ability to release drugs into the body in a regulated manner with low side effects, interact with a target site precisely, and facilitate faster drug absorption, nanotechnology and nanocarrier-based drug delivery systems have the potential to completely transform the treatment of degenerative illnesses(7). Many of the available treatments now have serious adverse effects or are unsuccessful. Anti-inflammatory medications, for example, may cause gastrointestinal upset, but neuroprotectants may cause neurotoxicity(8).

Nanoparticles are also an excellent option for treating these neurological and inflammatory conditions because of a number of benefits. Firstly, they could enhance the solubility and stability of medications, especially those with subpar pharmacokinetic characteristics(9). Secondly, drugs can be precisely delivered to the intended region of action by functionalizing nanoparticles to target certain brain tissues or cells. Third, a major obstacle to traditional medication administration to the central nervous system (CNS) is efficiently overcome by nanoparticles, which can traverse the blood-brain barrier (BBB). Anti-inflammatory medications have been effectively delivered to the brain using nano carrier systems to treat Alzheimer's disease (AD) and multiple sclerosis (MS). In a similar vein, neuroprotective medicines for Parkinson's disease have been administered to the brain via nanoparticles(10, 11).

Parkinson's Disease

A persistent, progressive extrapyramidal neurodegenerative illness is called Parkinson's disease (PD). PD often manifests between the ages of 55 and 62. Typically, 1.5% of people over 62 are impacted, and the incidence rises sharply as they age really well(12). The World Health Organization (WHO) estimates that 10 million people worldwide suffer with Parkinson's disease (PD), and that number is

predicted to rise to over 12 million in the next 30 years. Both the incidence and prevalence rate of the disease are predicted to rise by about 35%. Once the disease has advanced to the point where more than 60% of the dopaminergic neurons have already been destroyed, clinical symptoms typically appear(13).

The effects of compensatory biological processes, the cumulative effects of other pathologies, anatomic damage, and the ongoing changes in the neurotransmission synaptic system, particularly over usage of PD drugs result in a wide range of clinical symptoms among individuals. These symptoms comprise both motor and nonmotor symptoms, and they result in significant neuronal impairment. Tremors, abnormalities in speech and writing, slowed movement, and muscle rigidity are the most common motor signs. Cognitive, behavioural, and autonomic symptoms are examples of nonmotor manifestations. The majority of patients experience drug induced neuropsychiatric symptoms like dementia, anxiety disorders, sleep disorders, depression, sexual disorders, apathy, dysthymia and psychosis(14).

A wide range of clinical symptoms are caused by compensatory biological processes, the compounding effects of other illnesses, anatomic damage, and continuing alterations in the neurotransmission synaptic system, especially when PD medications are overused. Significant neuronal impairment is the outcome of these symptoms, which include both motor and nonmotor symptoms. The most typical motor indications include tremors, delayed movement, muscle rigidity, and difficulties in speaking and writing. Nonmotor manifestations include behavioral, autonomic, and cognitive problems. Drug-induced neuropsychiatric symptoms, including dementia, anxiety, insomnia, depression, sexual dysfunction, apathy, dysthymia, and psychosis, affect most patients. Most traditional medications come in oral dosage forms with little specificity to specific brain target sites. Only effective drug administration techniques can decrease negative effects caused by drugs while increasing patient compliance, brain specificity, and medication bioavailability(15).

Management of Parkinson's Disease

There are currently a number of medication therapies available to treat Parkinson's disease patients. They all have distinct indications, safety and efficacy profiles, and profiles. The restoration of dopaminergic neurons in the substantia nigra pars compacta and striatum is the primary goal of innovative approaches to treating Parkinson disease. Several pharmaceutical drugs drug treatment is used treatment for Parkinson's disease. Nevertheless, every medicine pas a unique set of drawbacks that could make it challenging to get the desired therapeutic effect. Thankfully, a new therapeutic strategy incorporating nanomedicines combining the medication with nanocarriers, it has significantly improved treatment outcomes(12).

The pharmacological properties of the medication have significantly improved as a result of this unique approach to administering it in an encapsulated form, and its half-life has also been extended. Among the additional therapeutic approaches for Parkinson's disease (PD) include immunotherapy, gene therapy, surgery, and behavioral therapy. After using medications for a long time, which caused drug-induced motor problems or maybe drug resistance in PD patients, surgical intervention was chosen as a therapy option. Electrodes are surgically inserted during deep brain stimulation, which has shown to be the

gold standard of care for certain individuals with severe Parkinson's disease. Deep brain stimulation includes pallidal stimulation, thalamic stimulation, and pedunculopontine nucleus stimulation(16).

The tremor was also treated with pallidotomy and thalamotomy, two alternative surgical procedures, although they were deemed less effective because of the increased risk of serious side effects. In addition to surgery, novel regenerative treatment modalities such as gene therapy, immunotherapy, and cell transplantation are making their way into clinical trials. Stem cells show promise as a treatment for Parkinson's disease (PD) in the future. When transplanting human embryonic stem cells (pluripotent) into a Parkinson's disease patient's striatum, these are the preferred cells. When dopaminergic neuronal cells from human embryonic mesencephalic cells were implanted into the midbrain of PD patients, the condition was significantly improved. A groundbreaking development in the treatment of Parkinson's disease is the insertion of disease-modifying transgenes that target the synthesis of dopamine and GABA(17).

Nanomedicine for Parkinson's Disease

Nanotechnology has attracted a lot of attention recently in treatment of PD. Nanoparticles are an excellent option for treating these neurological and inflammatory conditions because of a number of benefits. The use of nanomedicine has significantly enhanced medication delivery, diagnostic techniques, and the identification and management of a number of illnesses. When a medication is given through the systemic circulation, it is circulated throughout the body. Due to the drug's restricted capacity to cross the blood-brain barrier and its negative effects on body parts that are not impacted, this approach is not effective in healing CNS-associated diseases. Rapid advances in nanomedicine have made it possible for us to create ideal nanocarriers with the right drug loading and release dynamics(18). For the development of nanocarriers, it is imperative that they possess the following qualities: biodegradability, non-toxicity, prolonged drug release, particle size of less than 200 nm, drug encapsulation and release capabilities, and moieties that target the blood-brain barrier. Nanocarriers in the varied environment have well-maintained sizes, functionalized surfaces, and chemical characteristics. Nanocarriers therefore offer non-invasive ways to enhance drug localization and administration, hence boosting therapeutic dissolution and preservation across the BBB. Nanomedicine has broad applications in the treatment of cancer, diabetes, lung illnesses, inflammatory diseases, cardiovascular diseases, and neurological diseases. Additionally, imaging research makes substantial use of nanocarriers(19).

Shankar et al. described the applications of nanomedicine for treating Parkinson's disease. Parkinson's disease (PD) is a chronic, progressive neurological illness that is extrapyramidal in nature.With their extremely poor brain specificity, oral dose forms make up the majority of traditional treatments. Only effective brain-specific drug delivery strategies can improve bioavailability, patient compliance, and minimize unwanted side effects. We've evaluated the latest nanomedicines for Parkinson's disease (PD), their neurotherapeutic uses, and nanomedicines that incorporate phytopharmaceuticals. It is thought that PD patients' lives and lifestyles can be enhanced by nanomedicine(20). Hawthorne et al. explained that the nanomedicine will be overcome current Parkinson's treatment liabilities. It is possible to create and modify nanoparticles to have a wide range of characteristics. The designed nanomaterials possess many traits, such as the capacity to pass through the blood-brain barrier, due to their unique physicochemical characteristics.

They conducted a thorough analysis of many papers, outlining their possible contributions to the field of nanomedicine's involvement in boosting the effectiveness of established pharmacological treatments for Parkinson's disease. They explained how the nanocarrier system could be used to treat Parkinson's disease in the future(21). Van et al. focuses on the encapsulation of L-DOPA into authors' manufactured polymeric- and lipid-based nanoparticles (NPs) in order to increase the effectiveness of PD treatments and decrease adverse effects. These formulations can enhance the transport of L-DOPA to the central nervous system and shield it from systemic decarboxylation into DA. Furthermore, proteins, peptides, and antibodies that particularly target the blood-brain barrier (BBB) can be added to NPs to modify them and lower needed dosages and liberate systemic DA. Increased therapeutic DA concentrations in the brain are made possible by alternative delivery methods for NP-encapsulated L-DOPA, such as intravenous (IV), transdermal distribution utilizing adhesive patches, and direct intranasal administration. This review discusses the difficulties and potential directions for the field while giving a summary of recent developments in NP-mediated L-DOPA transport to the brain(22).

Mechanistic of Brain Targeting by Nanocarriers

Using polymer-coated nanocarriers, a number of innovative methods for target site drug delivery in the brain have been presented. Once administered, nanocarriers gather in the blood capillaries of the central nervous system. A concentration gradient is produced by the nanocarriers' adsorption and retention on the capillary walls. This causes the nanocarriers to diffuse past the layer of endothelial cells. The disintegration of endothelial cell layer fluids results in increased fluidization of the membrane. Neurotherapeutic drug delivery into the brain was a challenging problem for researchers until the discovery of drug-loaded nanocarrier administration. Because of its many benefits—which include BBB crossing, noninvasiveness, hepatic first-pass metabolism, simplicity of administration, safety, and usefulness—researchers are drawn to this mode of drug delivery(23, 24).

According to the study by Hernando et al., In the world, Parkinson's disease and Alzheimer's disease are the most prevalent neurodegenerative illnesses. Notwithstanding the scientific community's best efforts, the disease cannot be stopped from progressing; the present treatments are only moderately successful. For this reason, several compounds like metal chelators, growth hormones, and antioxidants have been proposed as potential therapeutics. Nevertheless, the therapeutic efficacy of these molecules is limited due to their inability to pass the blood-brain barrier. The creation of nanometric drug delivery systems may make it possible to distribute both new and existing medicines in a targeted and sustained manner, providing a fresh approach to treating these neurodegenerative illnesses(25). Zhao et al. prepared a NLRP3 (NOD-, LRR-, and pyrin domain-containing protein 3) inflammasome is a major target for medications used to treat Parkinson's disease (PD). In order to treat Parkinson's disease (PD), the authors create a carrier-free nanomedicine called NanoQC, which they derive from the naturally occurring phytochemical quercetin (QC). They show that NanoQC attenuates aberrant inflammasome assembly and activation by inhibiting NLRP3's deubiquitination and preventing its interaction with thioredoxin-interacting protein (TXNIP). This work offers new information for accurate target identification of nanomedicines and shows the enormous promise of using NanoQC to suppress the upstream pathways of NLRP3 inflammasome

assembly in the fight against Parkinson's disease(26). Srivastava et al. created highly pleiotropic melatonin-enriched polydopamine nanostructures that demonstrated effective brain tissue retention, sustained and extended melatonin release, and prevented neuroblastoma cell death induced by stimuli linked to Parkinson's disease and mitochondrial damage. The combined neuroprotection restored the potential of the mitochondrial membrane, decreased the production of reactive oxygen species (ROS) within the cell, prevented the activation of the caspase-dependent and independent apoptotic pathways, and demonstrated anti-inflammatory properties. Therefore, nature-inspired polydopamine nanostructures enhanced with melatonin that offer collective neuroprotective effects may be more suited for use in nanomedicine-based Parkinson's disease therapy because they activate anti-oxidative, anti-inflammatory, and anti-apoptotic pathways(27).

Inflammation

As a result of inherent sterile damage or foreign stimuli like infections, the host responds by becoming inflamed. It is typified by the recruitment and deposition of immune cells in areas of injury as well as the generation of soluble mediators such as chemokines, lipid mediators, reactive oxygen and nitrogen species, and cytokines. Although they are necessary for regulating inflammation and promoting tissue healing, these mediators have the potential to worsen tissue injury. Pattern recognition receptors (PRR) such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs), among others, sense pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) and initiate the inflammatory response by activating particular signaling pathways(28, 29).

Based on the stimuli and the pattern of the induced immune response, macrophages are among the most significant cells involved in the resolution or worsening of inflammation. Interleukin (IL)-1β receptors (TNFR and IL1R, respectively) and tumor necrosis factor (TNF)-α receptors (TNFR) activate macrophages, which in turn produces inflammatory mediators such nitric oxide (NO), TNF-α, IL-1β, IL-6, and cyclooxygenase (COX)-2. Inducible nitric oxide synthase (iNOS) generates macrophage-derived NO, which possesses immunomodulatory, anti-tumoral, and anti-pathogenic properties. High and persistent NO levels, however, are harmful to the host and play a role in the etiology of a number of illnesses. High amounts of TNF-α and IL-1β are also linked to inflammatory disorders. These substances affect immune cells autocrinely and paracrinely, intensifying the inflammatory response(30).

Inflammation is a normal and essential protective response to harmful stimuli such as antigen-antibody interactions, ischemia, physical agents, chemical, thermal, and viral agents. Inflammation is brought on by a number of factors, including as immunological responses, physical trauma, microbial invasion, and UV radiation. The typical hallmarks of inflammation are redness, warmth, swelling, and discomfort. Cascades of inflammation led to the development of diseases like multiple sclerosis, persistent asthma, arthritis, inflammatory bowel disease, and psoriasis. In our aging society, many of these ailments are crippling and are become increasingly prevalent(31).

Neuro-inflammatory disease, rheumatoid arthritis and degenerative arthritis are the two most common inflammatory diseases affecting people worldwide. Synthetic medications such as steroidal and non-steroidal anti-inflammatory drugs are primarily used to treat inflammation in order to repair the damages caused by this process. Synthetic medications such as NSAIDs and steroidal medicines, which

are frequently used for medication, are utilized to treat inflammation. These medications are frequently used to lessen inflammation by targeting its underlying cause. The doctors regularly prescribe these medications to relieve inflammation. Because of this, using it by people who are inflammatory can have serious adverse effects such gastrointestinal distress and liver damage. Therefore, there should be alternative medications that may treat inflammation with negligible or no adverse effects in order to prevent such major undesirable effects. We know that in the past, nanobased were used to treat similar symptoms caused by inflammation, which highlights the need for alternative therapies to cure inflammation(32, 33).

Drawbacks of Current Treatment Modalities for Inflammation

The traditional dose forms that are used to treat inflammation come with a number of difficulties. The main problems are caused by the medications' short half-lives, low bioavailability, poor solubility, and low patient compliance. Problems with drug-associated toxicity have also been noted for steroids and NSAIDs, two groups of anti-inflammatory medications. Conversely, biologics come with a higher price tag, a higher potential for adverse responses, and an increased risk of infection. Topical formulations, such as the aceclofenac-based dermal gel system, which has a rapid onset of action, increased drug release, and decreased stomach side effects/toxicity in patients with arthritis, have been developed to facilitate patient compliance(34).

However, the use of these gel formulations has been restricted due to the quick degradation of the active ingredients by skin-resident enzymes. Consequently, the development of affordable, minimally hazardous inflammatory treatments is necessary. At this time, safer and more potent drugs are being investigated for the treatment of inflammation. Another strategy is to create innovative dosage forms to guarantee continuous and extended drug administration. It might aid in lessening drug toxicity as well as problems with the medications' short half-lives, low bioavailability, and poor solubility(35).

Nanoparticle Targeting with Inflammatory Molecules

Since nonresolving inflammation is not only a response cause but also plays a major role in the pathogenesis of many degenerative diseases, such as obesity, atherosclerosis, asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, inflammatory bowel disease, cardiovascular neurodegenerative diseases, cancer, and sepsis, it has been a major area of focus for the past few decades to suppress inflammation and inflammatory responses. An accurate and sensitive identification of the inflammatory location may have a significant influence on the prognosis and management of the illness(36). The endothelium expresses higher levels of many adhesion molecules in response to inflammation. Immune cells interact with these molecules through counter-adhesion molecules like integrins, which stick to endothelium and cause diapedesis. By using peptides or antibodies specific to adhesion molecules including collagen, intracellular adhesion molecules (ICAM), vascular cell adhesion molecules (VCAM), and the immunoglobulin super family, researchers are hoping to use nanoparticles for the detection and therapy of inflammation(37). Despite its constitutive low level expression, ICAM has garnered special attention among these molecules due to its localized expression upon inflammatory signals, which can act as a marker for inflammation(38). The leucocyte integrins CD11/CD18 are bound by the five members of

the ICAM family, which are identified as ICAM-1 to ICAM-5. This binding occurs during immunological responses and inflammation. Once more, ICAMs may be present in soluble forms in human plasma as a result of activation processes at cell surfaces and proteolysis. On the other hand, leucocytes can be drawn to inflammatory areas by VCAM binding to leucocyte integrin VL-4 (very late antigen-4). An innovative approach has been created by a group of scientists at Harvard Medical School in Boston using liposome-based targetable nanoparticles loaded with the cell cycle regulating molecule cyclin D1siRNA(39). For improved nucleic acid delivery, Si RNA has also been coupled with the positively charged protein protamine. It has been shown that when monoclonal antibodies like F1B504 are coupled to hyaluronan liposome nanoparticles, they bind integrin. Various nanocarriers system also available to treat inflammatory conditions(40, 41).

Zhu et al. worked on treatment of inflammation in CNS. An inflammatory reaction inside the central nervous system (CNS) is called neuroinflammation. Treating neurodegenerative illnesses by inhibiting microglia over-activation and microglia-mediated neuroinflammation has shown promise. Anti-inflammatory medications have been found to be effectively transported by several nanacarrier systems across the blood-brain barrier to prevent neuroinflammation and excessive microglia activation. Therefore, it is possible to produce NPs with good biodegradability and biocompatibility as a therapeutic agent for neuroinflammation-mediated neurodegenerative illnesses or as an efficient, less invasive carrier to enable other medications pass the blood-brain barrier(42). Ulbrich et al. described the targeted drug-delivery approaches by nanoparticulate carriers in the therapy of inflammatory diseases. Many amazing strategies have been discovered to treat inflammatory illnesses. When it comes to getting the drug load to the site of action, almost all systems show a better specificity. Selective medication delivery to inflammatory barriers is a promising application of nanocarriers. To develop particular and disease-related adhesion mechanisms, more research is required as the precise target cells remain unknown. Up until recently, passive targeting methods have been the foundation of the therapeutic choices that seem closest to clinical usage(43). Garg et al. prepared Nanostructured lipid carrier–mediated transdermal aceclofenac hydrogel for inflammatory diseases. A cyclooxygenase-2 inhibitor, aceclofenac (ACE) is a diclofenac group derivative used to treat rheumatoid arthritis (RA), a systemic inflammatory autoimmune disease, symptomatically. Its high lipophilicity, partial solubility, and stability make it difficult to employ in topical formulation development. Therefore, in order to achieve effective transdermal administration, the scientists created and described an ACE hydrogel based on nanostructured lipid carriers (NLC) (ACE-NLC). The ACE-NLC-gel formulation demonstrated improved skin dispersion in the dermis and epidermis as well as good rheological and textural properties. Furthermore, ACE-NLC maintained the integrity of the skin by penetrating deeper into the skin layers. Comparing the NLC-based gel formulation of ACE to the traditional Mkt-gel formulation, the latter may represent a more promising nanoscale lipid carrier for topical delivery(44). Sharma et al. combined a aceclofenac with lysine (LYS) and developed aceclofenac–LYS cocrystal. It was then encapsulated in liposome lipid bilayers using a dual carrier technique to treat rheumatoid arthritis (RA) pain-related problems. Furthermore, it was discovered that the hydrogel-incorporated nanoproduct was significantly compatible with rodent skin and rheologically acceptable. According to the investigations, LYS-conjugated

liposome-entrapped nanocarriers are better than the commercial product at managing disorders like RA(45).

Nano Carrier-based Drug Delivery System

A new method called nanotechnology uses a variety of tools and techniques to administer medicinal agents and diagnose diseases. Targeted at macrophages, drug-loaded nanoparticles have been employed as an anti-inflammatory agent. Nanoparticles have a tendency to collect in the liver and spleen, which are components of the reticuloendothelial system (RES)(46). This characteristic is used in the creation of medications based on nanoformulations to treat inflammation. Researchers concentrate on creating nanoparticle-based delivery systems for medications whose hydrophilic gastrointestinal tract environments cause problems with oral bioavailability. Researchers have experimented with modifying chemical entities, using proteolytic enzyme inhibitors and permeation enhancers, reducing hepatic first-pass metabolism, modulating gastrointestinal transit time, and developing novel drug delivery strategies in an attempt to overcome obstacles and increase drug bioavailability(47, 48).

Drugs delivered in nanocarriers have the potential to improve circulation time, decrease clearance, prolong residence duration and half-life, and prevent pre-systemic metabolism at the absorption site, according to research on their pharmacokinetics. Because of their ability to regulate their size, shape, charge, and lipophilicity, the nanocarriers are able to more easily cross the GI membrane(49). Different nanoparticulate systems, including lipid-based drug delivery systems, quantum dots, dendrimers, metal-oxide nanoparticles, microcapsules, cells, cell ghosts, lipoproteins, and diverse nanoassemblies are all included in the field of nanotechnology. Drugs can be administered orally using a nanoparticle method to increase their therapeutic index, specificity, tolerance, and efficacy(50).

Advantages of Nanocarrier Drug Delivery for Neuroinflammatory and Neurodegenerative Diseases

Neuroinflammatory and neurodegenerative illnesses, which are marked by a progressive loss of neurons and a deterioration in behavior, motor control, and cognitive function, constitute a substantial public health burden. While some standard treatments do work, they usually merely slow the disease's course and do not completely heal the underlying damage(51).

Nano carrier is becoming a viable tactic in this difficult situation. When it comes to medicine delivery for neuroinflammatory and neurodegenerative illnesses, nanoparticles have many benefits. They do this by first increasing a drug's solubility and stability, which is crucial for medications with low solubility or stability because it keeps them from degrading and increases their therapeutic efficacy. Secondly, drugs may be precisely delivered to particular cells or tissues, including the central nervous system, thanks to nanoparticles(52). Nanoparticles can minimize off-target effects by binding to cell surface receptors or markers by altering them with ligands or antibodies. Third, the BBB presents a considerable barrier to drug delivery to the central nervous system that is overcome by nanoparticles(53). The BBB can be broken or crossed by engineered nanoparticles, which makes effective medication administration possible. Nanoparticles can be transported across the BBB with the aid of tactics including BBB disruption, active targeting, and passive targeting(54). Furthermore, as controlled and sustained drug

release is crucial for the treatment of chronic neuroinflammatory and neurodegenerative illnesses, nanoparticles extend the duration of therapeutic effects and minimize the frequency of administration. Furthermore, nanoparticles can be used to deliver combination therapy or numerous medications, which can have a synergistic effect and improve outcomes. This is particularly useful for complicated disorders involving multiple targets or processes(55, 56).

The development of novel therapeutics to prevent and treat diseases resulting from the interplay between neuroinflammation and neurodegeneration depends on our ability to comprehend the molecular and cellular mechanisms underlying this interplay. To prevent cellular damage to neurons and regulate the neuroinflammatory response, several nanotechnological treatments have also been created(57). For neuroinflammatory and neurodegenerative illnesses, in summary, nanoparticle-based drug delivery (NDD) has advantages such enhanced drug solubility and stability, targeted administration, blood-brain barrier penetration, prolonged release, and possibility for combination therapy. This strategy seems like a good fit for handling these difficult circumstances(58, 59).

Patents Related to Nano Carrier System

Patent Number	**Title of Patents**	**Summary**	**Inventor and Year of Application**
CN111603565A	Anti-inflammatory nano-drug carrier, pharmaceutical composition thereof, preparation method and application	The invention describes a double-block polymer made of choline polyphosphate and poly (methylthio ethyl acrylate) that functions as an anti-inflammatory nano-drug carrier, together with the drug composition, preparation technique, and application. Anti-inflammatory drugs that have been specifically formulated have a function in both diagnosis and therapy, and they are effective in both for acute and chronic inflammation, including atherosclerosis, arthritis, pneumonia, and other conditions.	Wang Yunbing Ma Boxuan, 2020
CN1682704A	Levodopa nano preparation and its preparing method	The current invention is related to medical preparation, specifically a type of nanomedicine preparation that treats Parkinson's disease and Parkinson's syndrome by using polymer as a carrier and levodopa as an effective component. The manufacture of nanoscale levodopa is made by first synthesizing the hydrophilic block	Zhou Wenbin Liu Xiaoying, 2004

		copolymer PEO-b-PAA, and then loading the nanometer levodopa particle.	
CN101879153A	Levodopa methyl ester and benserazide mixed medicament slow-release microsphere composition and preparation method thereof	The levodopa methyl ester and benserazide combination medication slow-release microsphere formulation is the subject of the invention. The following elements make up the composition, expressed as a percentage of weight: 50 to 99 percent degradable hydrophobic polymer and 1 to 50 percent combination medication containing benserazide and levodopa methyl ester, with a weight ratio of 1:1–4:1. Additionally, a technique for preparing the combined medication slow-release microsphere composition is provided by the invention.	Liu Zhenguo, Yuan Weien, Ren Tiantian, Yang Xinxin, Chen Wei, 2010
CN101879143A	Microsphere combination medicament containing antiparkinsonism drug and application thereof	The invention is related to the use of a microsphere composition that contains an antiparkinsonian medication in the creation of a medication intended to treat and prevent Parkinson's disease as well as to exacerbate its symptoms. The invention's microsphere combination medication, which contains the antiparkinsonian medicine, is a safe, nontoxic drug with a potent pharmacological effect and promising therapeutic potential.	Liu Zhenguo, Yuan Weien, 2010
WO2012009973A1	Antiparkinsonian drug-loaded microsphere composition and use thereof	The preparation of a medication for the prevention or treatment of Parkinson's disease or its complications using a composition of antiparkinsonian drug-loaded microspheres is disclosed.	Liu Zhenguo Yuan Weien, 2011
CN101884623B	Levodopa methyl ester slow-release microsphere composition and preparation method thereof	The invention is related to a slow-release microsphere composition of levodopa methyl ester that contains, by weight percentage, 1 to 50% of levodopa methyl ester and 50 to 99 percent of degradable hydrophobic polymer.	Liu Zhenguo, 2010

CN112274651B	Polydopamine nano-carrier delivery system for targeted activation of CD44 molecules, preparation method and application thereof	With the help of a targeting ligand that can specifically bind to the activated CD44 molecule, the surface of the polydopamine nanocarrier is partially modified in the present invention to provide a delivery system for targeted activation of CD44 molecules. Benefits of the nano-carrier and its synthesis method include high drug loading capacity, ease of use with a variety of medicines, high yield, easy process, and ease of coupling different targeting ligands.	Ma Qian Sun Jiefang, 2020
CN1965819A	Nanoemulsion of aceclofenac for treating rheumatoid arthritis and preparation process thereof	Aceclofenac 0.10–3.00%, solvent 1.00–10.00%, surface active agent 15.00–40.00%, auxiliary surface active agent 0.00–15.00%, oil 5.00–20.00%, penetration enhancer 0.00–5.00%, and balancing distilled water are all disclosed in the invention for the purpose of treating rheumatoid arthritis.	Ouyang Wuqing He Xin, 2006
CN111110630A	Novel blood brain barrier crossing drug delivery system and preparation method and application thereof	The innovation is related to drug delivery systems, specifically to a new drug delivery system that crosses the blood brain barrier, as well as to its production and use. Polydopamine nanoparticles are encapsulated in micelles of amphiphilic peptides as part of a unique cross-blood brain barrier medication delivery method.	Liu Zhe, Zhang Chen, 2020
CN113925834B	Polydopamine-lactoferrin drug carrier and application thereof	The innovation deals with the use of a polydopamine-lactoferrin medication carrier. The drug carrier polydopamine-lactoferrin is a nanoparticle that can cross the blood-brain barrier, exhibit targeting ability, raise the pH of an acidic environment, disintegrate post-treatment, and does not produce cumulative toxicity.	Shenzhen Second Peoples Hospital,
US9579400B2	Nanocarriers for drug delivery	The nanocarrier of the present invention has an exterior and an interior, and it includes at least one conjugate, each of which contains a polyethylene glycol (PEG) polymer. At least	Kit S. Lam, Juntao Luo, 2009

		two amphiphilic molecules with hydrophilic and hydrophobic faces are also present in each conjugation. Every conjugate also consists of an oligomer, to which at least two amphiphilic chemicals are covalently bonded. The oligomer is then covalently attached to the PEG.	
EP3474864 A1	Nanostructurated lipid carriers, methods and uses thereof	The current disclosure focuses on novel, highly successful treatments for diseases caused by Helicobacter pylori. These treatments include nanostructured lipid carriers (NLCs), which are particles of imperfect crystal type, solid amorphous type (non-crystalline matrix), or multiple type. The current disclosure also relates to a process for producing such nanoparticles as well as compositions that contain them.	Catarina LEAL SEABRA, Cláudia Daniela OLIVEIRA, 2017
KR1020811 92B1	Novel drug carriers for oral administration of drugs difficult to oral administration and preparation method thereof	The novel drug carriers or pharmaceutically acceptable salts thereof made possible by the current invention make it easier to administer medications orally to patients who have oral health issues. When taken orally in conjunction with a medication that is challenging to take orally, the drug carrier or pharmaceutically acceptable salt of the present invention exhibits an excellent body absorption rate without compromising the biological activity of the drug and can be prepared with only a brief manufacturing step. It has many benefits for large-scale manufacturing.	Kim Kyung-jin, Yoon-ji, Sook-jeong, 2015
EP2793953 B1	Telodendrimers with enhanced drug delivery	The invention additionally provides a nanocarrier with an exterior and an interior that is made up of several of the invention's compounds. Each compound self-assembles in an aqueous solvent to form the nanocarrier, forming a hydrophobic pocket in its interior,	University of California, 2012

		and each compound's PEG self-assembles on its exterior.	
WO2021030743A3	Smart peptides and transformable nanoparticles for cancer immunotherapy	A hydrophobic moiety (A), a peptide (B) that forms a beta-sheet, and a hydrophilic targeting ligand (C) that can be any of the following: an LLP2A prodrug, LLP2A, LXY30, LXW64, DUPA, folate, an LHRH peptide, a HER2 ligand, an EGFR ligand, or a toll-like receptor agonist CpG oligonucleotides. This invention is made possible by the compound formula (I): A-B-C (I). Additionally, the present invention offers techniques for using nanocarriers for imaging and disease treatment, as well as nanocarriers made of the current invention's compounds and capable of forming nanofibrils.	Kit S. LamLu Zhang, 2020
WO2021092225A3	Nanoparticles comprising prodrugs stabilized by albumin for treatment of cancer and other diseases	Pharmaceutical compositions containing solid nanoparticles are provided by the present invention. The solid nanoparticles consist of two components: i) an effective concentration of a therapeutically active agent, such as a prodrug that is largely water insoluble; and ii) a biocompatible polymer.	Ulagaraj Selvaraj, David Woody, 2020
US10842755B2	Nanoparticles for brain targeted drug delivery	There is a nanoparticle available that can be used to transfer an active ingredient via the blood-brain barrier. Because of this, the nanoparticle can specifically target brain tissue, allowing the active drug to pass through the blood-brain barrier and reach the intended location in the brain. The nanoparticle consists of a shell made of a membrane taken from a brain metastatic cancer cell, which helps the nanoparticle pass through the blood-brain barrier. The core of the nanoparticle consists of an active agent and a polymer or inorganic material. The	Peisheng Xu, 2019

		techniques for creating and utilizing the nanoparticle are also provided.	

Safety Profile and Future Prospective of Nano Carrier System

The complete in vivo potential of nanotechnology, and specifically nanomedicine, depends on the completion of toxicity studies. Knowledge of the physicochemical, molecular, and physiological processes of nanoparticles is essential for nanomedicine to become a dependable and sustainable treatment modality(60). Additional research is required to ascertain the biodistribution of nanoparticles following skin and GI tract exposure. Numerous pre-clinical studies have shown a decreased toxicity profile when anti-inflammatory and various anti-Parkinson's drugs are incorporated into nanocarrier systems in rodent studies(61). Despite the advances in nanotoxicology in recent years, scientists are still unable to accurately predict the behavior and biokinetics of nanoparticles.

The drug delivery applications have been extensively studied using nanoparticulate technology, which has seen significant advancements in recent decades. The goal of developing nanoparticulate systems is to address the shortcomings and restrictions of traditional dosage forms(62). The similar concept is used when discussing nanoparticles for oral drug delivery systems, when the goal is to get around restrictions on the medication's stability, permeability through biological barriers, and solubility. The largest obstacle to creating a secure and effective drug delivery system is the paucity of toxicity and safety evaluations of oral nanoparticulate systems, despite the huge quantity of research on the subject(63). Furthermore, research must be done to determine how each characteristic of the nanoparticle system—such as size, charge, and surface chemistries—affects toxicity. To provide comprehensive toxicity safety profiles for each system, in-depth research is necessary. This will help meet the strict requirements set by regulatory bodies and expedite approval(64). Strong collaboration between toxicologists and formulation scientists can help overcome the paucity of information on the safety and toxicity of nanoparticles(65). Furthermore, trying to include these toxicity studies from the outset of the formulation development process can help create safer formulations later on.

Conclusion

The three most prevalent inflammatory disorders impacting people globally are degenerative arthritis, rheumatoid arthritis, and neuro-inflammatory disease. Due to neuronal loss and diminished brain function, nano carrier systems are becoming a viable treatment option for neuroinflammatory and neurodegenerative illnesses, which pose a serious threat to public health. Many medications and therapies have been developed to treat degenerative arthritis, rheumatoid arthritis, and inflammatory diseases; however, these have often been linked to adverse effects like drug resistance, poor solubility, decreased bioavailability, and inability to cross the blood–brain barrier (BBB). Due to several advantages, nanoparticles are a great choice for the treatment of various inflammatory and neurological diseases. Additionally, they reduce unfavorable side effects by enabling the exact delivery of medications to particular CNS cells or tissues. They use passive/active targeting and BBB disruption to get around a

critical BBB that prevents effective medication delivery to the central nervous system. Furthermore, the controlled and prolonged release of medications made possible by nanoparticles lowers the frequency of administration—a crucial factor for chronic illnesses. Lastly, its capacity to deliver several medications or combination treatments fosters synergistic effects, which are particularly advantageous for complicated illnesses. Significant improvements to nano regulation are still being made to address safety, pharmacological, environmental, and health concerns. The serious and careful study of the environment, health, and safety as well as the relevant and transparent debate on the wider societal implications of toxicological and pharmacological issues are necessary for the swift commercialization of nanotechnology.

References

1. Manji H, Sisodiya S. Global Burden of Neurological Disease and the Neurology of Climate Change. Neurology: A Queen Square Textbook. 2024:1-15.

2. Bengoechea-Fortes SdlP, Ramírez-Expósito MJ, Martínez-Martos JM. Suicide, neuroinflammation and other physiological alterations. European archives of psychiatry and clinical neuroscience. 2024;274(5):1037-49.

3. Rim C, You M-J, Nahm M, Kwon M-S. Emerging role of senescent microglia in brain aging-related neurodegenerative diseases. Translational Neurodegeneration. 2024;13(1):10.

4. Xu T, Dong W, Liu J, Yin P, Wang Z, Zhang L, et al. Disease burden of Parkinson's disease in China and its provinces from 1990 to 2021: findings from the global burden of disease study 2021. The Lancet Regional Health–Western Pacific. 2024;46.

5. Golsorkhi M, Sherzai A, Dashtipour K. The Influence of Lifestyle on Parkinson's Disease Management. Lifestyle Medicine, Fourth Edition: CRC Press. p. 919-24.

6. Samim KS, Naren P, Pinjala P, Uppala S, Singh SB, Khatri DK. Pathophysiology and Management Approaches for Parkinson’s Disease. Drug Delivery Strategies in Neurological Disorders: Challenges and Opportunities: Springer; 2024. p. 103-53.

7. Shirsath NR, Goswami AK. Nanocarriers based novel drug delivery as effective drug delivery: a review. Current Nanomaterials. 2019;4(2):71-83.

8. Raikwar S, Jain SK. Nano-Based Drug Delivery System: An Overview and Future Prospective. Smart Nanocarrier for Effective Drug Delivery.126-43.

9. Asefy Z, Hoseinnejhad S, Ceferov Z. Nanoparticles approaches in neurodegenerative diseases diagnosis and treatment. Neurological Sciences. 2021;42(7):2653-60.

10. Sim TM, Tarini D, Dheen ST, Bay BH, Srinivasan DK. Nanoparticle-based technology approaches to the management of neurological disorders. International Journal of Molecular Sciences. 2020;21(17):6070.

11. Cano A, Sanchez-Lopez E, Ettcheto M, Lopez-Machado A, Espina M, Souto EB, et al. Current advances in the development of novel polymeric nanoparticles for the treatment of neurodegenerative diseases. Nanomedicine. 2020;15(12):1239-61.

12. Bloem BR, Okun MS, Klein C. Parkinson's disease. The Lancet. 2021;397(10291):2284-303.

13. Tolosa E, Garrido A, Scholz SW, Poewe W. Challenges in the diagnosis of Parkinson's disease. The Lancet Neurology. 2021;20(5):385-97.

14. Jankovic J, Tan EK. Parkinson's disease: etiopathogenesis and treatment. Journal of Neurology, Neurosurgery & Psychiatry. 2020;91(8):795-808.

15. McFarthing K, Rafaloff G, Baptista M, Mursaleen L, Fuest R, Wyse RK, et al. Parkinson's disease drug therapies in the clinical trial pipeline: 2022 update. Journal of Parkinson's disease. 2022;12(4):1073-82.

16. Sharma VD, Patel M, Miocinovic S. Surgical treatment of Parkinson's disease: devices and lesion approaches. Neurotherapeutics. 2020;17(4):1525-38.

17. Young C, Phillips R, Ebenezer L, Zutt R, Peall KJ. Management of Parkinson's disease during pregnancy: Literature review and multidisciplinary input. Movement Disorders Clinical Practice. 2020;7(4):419-30.

18. Padilla-Godínez FJ, Ruiz-Ortega LI, Guerra-Crespo M. Nanomedicine in the face of Parkinson's disease: from drug delivery systems to nanozymes. Cells. 2022;11(21):3445.

19. Sharma S, Rabbani SA, Agarwal T, Baboota S, Pottoo FH, Kadian R. Nanotechnology driven approaches for the management of Parkinson's disease: current status and future perspectives. Current drug metabolism. 2021;22(4):287-98.

20. Shankar J, Geetha K, Wilson B. Potential applications of nanomedicine for treating Parkinson's disease. Journal of Drug Delivery Science and Technology. 2021;66:102793.

21. Hawthorne GH, Bernuci MP, Bortolanza M, Tumas V, Issy AC, Del-Bel E. Nanomedicine to overcome current Parkinson's treatment liabilities: A systematic review. Neurotoxicity research. 2016;30:715-29.

22. van Vliet EF, Knol MJ, Schiffelers RM, Caiazzo M, Fens MH. Levodopa-loaded nanoparticles for the treatment of Parkinson's disease. Journal of Controlled Release. 2023;360:212-24.

23. Han L, Jiang C. Evolution of blood–brain barrier in brain diseases and related systemic nanoscale brain-targeting drug delivery strategies. Acta Pharmaceutica Sinica B. 2021;11(8):2306-25.

24. Khatoon R, Alam MA, Sharma PK. Current approaches and prospective drug targeting to brain. Journal of Drug Delivery Science and Technology. 2021;61:102098.

25. Hernando S, Gartziandia O, Herran E, Pedraz JL, Igartua M, Hernandez RM. Advances in nanomedicine for the treatment of Alzheimer's and Parkinson's diseases. Nanomedicine. 2016;11(10):1267-85.

26. Zhao D, Tian C, Cheng M, Yang F, Tian C, Liu Y, et al. Carrier-free quercetin nanomedicine blocks NLRP3 deubiquitination and TXNIP recruitment for Parkinson's disease therapy. Chemical Engineering Journal. 2023;464:142697.

27. Srivastava AK, Choudhury SR, Karmakar S. Melatonin/polydopamine nanostructures for collective neuroprotection-based Parkinson's disease therapy. Biomaterials science. 2020;8(5):1345-63.

28. Pezone A, Olivieri F, Napoli MV, Procopio A, Avvedimento EV, Gabrielli A. Inflammation and DNA damage: cause, effect or both. Nature Reviews Rheumatology. 2023;19(4):200-11.

29. Netea MG, Balkwill F, Chonchol M, Cominelli F, Donath MY, Giamarellos-Bourboulis EJ, et al. A guiding map for inflammation. Nature immunology. 2017;18(8):826-31.

30. Bae J-Y, Lee D-S, Cho YK, Lee J-Y, Park J-H, Lee SH. Daphne jejudoensis attenuates LPS-induced inflammation by inhibiting TNF-α, IL-1β, IL-6, iNOS, and COX-2 expression in periodontal ligament cells. Pharmaceuticals. 2022;15(4):387.

31. Actor JK, Smith KC. Translational inflammation. Translational Inflammation: Elsevier; 2019. p. 1-22.

32. Sarzi-Puttini P, Pellegrino G, Giorgi V, Bongiovanni SF, Varrassi G, Di Lascio S, et al. Inflammatory or non-inflammatory pain in inflammatory arthritis–How to differentiate it? Best Practice & Research Clinical Rheumatology. 2024:101970.

33. Jeon KH, Han K, Jung J, Park CI, Eun Y, Shin DW, et al. Rheumatoid Arthritis and Risk of Depression in South Korea. JAMA Network Open. 2024;7(3):e241139-e.

34. Simon MS, Arteaga-Henríquez G, Fouad Algendy A, Siepmann T, Illigens BM. Anti-inflammatory treatment efficacy in major depressive disorder: a systematic review of meta-analyses. Neuropsychiatric Disease and Treatment. 2023:1-25.

35. Radu A-F, Bungau SG. Nanomedical approaches in the realm of rheumatoid arthritis. Ageing research reviews. 2023;87:101927.

36. Wang X, Xia Z, Wang H, Wang D, Sun T, Hossain E, et al. Cell-membrane-coated nanoparticles for the fight against pathogenic bacteria, toxins, and inflammatory cytokines associated with sepsis. Theranostics. 2023;13(10):3224.

37. Liu J, Liu Z, Pang Y, Zhou H. The interaction between nanoparticles and immune system: application in the treatment of inflammatory diseases. Journal of Nanobiotechnology. 2022;20(1):127.

38. Jogdeo CM, Panja S, Kanvinde S, Kapoor E, Siddhanta K, Oupický D. Advances in lipid-based codelivery systems for cancer and inflammatory diseases. Advanced healthcare materials. 2023;12(7):2202400.

39. Wang H, Zhou Y, Sun Q, Zhou C, Hu S, Lenahan C, et al. Update on nanoparticle-based drug delivery system for anti-inflammatory treatment. Frontiers in Bioengineering and Biotechnology. 2021;9:630352.

40. Puricelli C, Gigliotti CL, Stoppa I, Sacchetti S, Pantham D, Scomparin A, et al. Use of poly lactic-co-glycolic acid nano and micro particles in the delivery of drugs modulating different phases of inflammation. Pharmaceutics. 2023;15(6):1772.

41. Li W, Yu L, Li W, Ge G, Ma Y, Xiao L, et al. Prevention and treatment of inflammatory arthritis with traditional Chinese medicine: underlying mechanisms based on cell and molecular targets. Ageing Research Reviews. 2023;89:101981.

42. Zhu F-D, Hu Y-J, Yu L, Zhou X-G, Wu J-M, Tang Y, et al. Nanoparticles: A Hope for the Treatment of Inflammation in CNS. Frontiers in Pharmacology. 2021;12:683935.

43. Ulbrich W, Lamprecht A. Targeted drug-delivery approaches by nanoparticulate carriers in the therapy of inflammatory diseases. Journal of The Royal Society Interface. 2010;7(suppl_1):S55-S66.

44. Garg NK, Tandel N, Bhadada SK, Tyagi RK. Nanostructured lipid carrier–mediated transdermal delivery of aceclofenac hydrogel present an effective therapeutic approach for inflammatory diseases. Frontiers in Pharmacology. 2021;12:713616.

45. Sharma G, Saini MK, Thakur K, Kapil N, Garg NK, Raza K, et al. Aceclofenac cocrystal nanoliposomes for rheumatoid arthritis with better dermatokinetic attributes: a preclinical study. Nanomedicine. 2017;12(6):615-38.

46. Shi Z, Zhou Y, Fan T, Lin Y, Zhang H, Mei L. Inorganic nano-carriers based smart drug delivery systems for tumor therapy. Smart Materials in Medicine. 2020;1:32-47.

47. Qamar Z, Qizilbash FF, Iqubal MK, Ali A, Narang JK, Ali J, et al. Nano-based drug delivery system: recent strategies for the treatment of ocular disease and future perspective. Recent Patents on Drug Delivery & Formulation. 2019;13(4):246-54.

48. Spandana KA, Bhaskaran M, Karri VR, Natarajan J. A comprehensive review of nano drug delivery system in the treatment of CNS disorders. Journal of Drug Delivery Science and Technology. 2020;57:101628.

49. Sultana A, Zare M, Thomas V, Kumar TS, Ramakrishna S. Nano-based drug delivery systems: Conventional drug delivery routes, recent developments and future prospects. Medicine in Drug Discovery. 2022;15:100134.

50. Nath R, Roy R, Barai G, Bairagi S, Manna S, Chakraborty R. Modern developments of nano based drug delivery system by combined with phytochemicals-presenting new aspects. Int J Sci Res Sci Technol. 2021;8:107-29.

51. Ozceylan O, Sezgin-Bayindir Z. Current Overview on the Use of Nanosized Drug Delivery Systems in the Treatment of Neurodegenerative Diseases. ACS Omega. 2024.

52. Keshavarz Shahbaz S, Koushki K, Keshavarz Hedayati S, McCloskey AP, Kesharwani P, Naderi Y, et al. Polymer nanotherapeutics: A promising approach toward microglial inhibition in neurodegenerative diseases. Medicinal Research Reviews.

53. Yergök RA, Derman S, Alakbarli J, Eskhıta AS. Brain-Targeted Nano-Drug Delivery for the Treatment of Parkinson's Disease. Current Research in Health Sciences. 2024;1(2):77-92.

54. Rana P, Kaur G, Chirayimmel AJ, Rajput A, Rath SK, Dwibedi V. Nanocarriers and Nano Drug Delivery Therapy in Neuro Diseases. Nanomaterials for Drug Delivery and Neurological Diseases Management: Springer; 2024. p. 219-51.

55. Singh K, Sethi P, Datta S, Chaudhary JS, Kumar S, Jain D, et al. Advances in Gene Therapy Approaches Targeting Neuro-inflammation in Neurodegenerative Diseases. Ageing Research Reviews. 2024:102321.

56. Xie A, Cheng G, Wu J, Li Z, Yu G, Zhu X, et al. Highly BBB-Permeable Nanomedicine Reverses Neuroapoptosis and Neuroinflammation to Treat Alzheimer's Disease. Biomaterials. 2024:122749.

57. Sahu T, Ratre YK, Chauhan S, Bhaskar L, Nair MP, Verma HK. Nanotechnology based drug delivery system: Current strategies and emerging therapeutic potential for medical science. Journal of Drug Delivery Science and Technology. 2021;63:102487.

58. Ferrão R, Rai A. Advanced Polymeric Nanoparticles for the Treatment of Neurodegenerative Diseases. Chemical Physics of Polymer Nanocomposites: Processing, Morphology, Structure, Thermodynamics, Rheology. 2024;3:843-85.

59. Song X, Zhang Y, Tang Z, Du L. Advantages of nanocarriers for basic research in the field of traumatic brain injury. Neural regeneration research. 2024;19(2):237-45.

60. Unnithan D, Sartaj A, Iqubal MK, Ali J, Baboota S. A neoteric annotation on the advances in combination therapy for Parkinson's disease: nanocarrier-based combination approach and future anticipation. Part II: nanocarrier design and development in focus. Expert opinion on drug delivery. 2024;21(3):437-56.

61. Manu K, Kaur G, Kar A, Giri L, Almalki WH, Gupta N, et al. Future prospect of nano-based drug delivery approaches against pancreatic cancer and expected pitfalls of the technology. Recent Advances in Nanocarriers for Pancreatic Cancer Therapy: Elsevier; 2024. p. 419-42.

62. Peng S, Wang W, Zhang R, Wu C, Pan X, Huang Z. Nano-formulations for pulmonary delivery: Past, present, and future perspectives. Pharmaceutics. 2024;16(2):161.

63. Fatima I, Zeinalilathori S, Qindeel M, Kharab Z, Sahebzade MS, Rahdar A, et al. Advances in Targeted Nano-Delivery of Bevacizumab Using Nanoparticles: Current Insights, Innovations, and Future Perspectives. Journal of Drug Delivery Science and Technology. 2024:105850.

64. Mahajan K, Bhattacharya S. The Advancement and Obstacles in Improving the Stability of Nanocarriers for Precision Drug Delivery in the Field of Nanomedicine. Current Topics in Medicinal Chemistry. 2024;24(8):686-721.

65. Alshawwa SZ, Kassem AA, Farid RM, Mostafa SK, Labib GS. Nanocarrier drug delivery systems: characterization, limitations, future perspectives and implementation of artificial intelligence. Pharmaceutics. 2022;14(4):883.