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Targeted Delivery of Omega-3 Fatty Acids using Cyclodextrin-Based Nanosponges: Therapeutic Potential in Neurodegenerative Diseases

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Abstract
The increasing incidence of neurodegenerative diseases including multiple sclerosis, Parkinson's disease, and Alzheimer's disease worldwide has brought attention to the need for efficient therapeutic treatments. Among other potential nutraceuticals, omega-3 fatty acids have become potent neuroprotective agents because of their anti-inflammatory, antioxidant, and membrane-stabilizing properties. However, oxidative instability, limited bioavailability, poor water solubility, and non-specific distribution in the central nervous system (CNS) hinder their therapeutic use. To overcome these limitations, novel nanocarrier systems are being explored, among which cyclodextrin-based nanosponges (CD-NS) have gained significant attention. This review explores the innovative application of CD-NS as an advanced platform for the targeted delivery of Omega-3 fatty acids to the brain. Cyclodextrins, with their unique hydrophilic outer surface and hydrophobic core, facilitate encapsulation of lipophilic molecules like Omega-3s, while nanosponge cross-linking enhances stability, controlled release, and brain-specific targeting. We critically discuss the synthesis strategies, physicochemical characteristics, and surface modifications of CD-NS that improve blood-brain barrier permeability and prolong systemic circulation. Furthermore, this paper elaborates on mechanistic insights into how Omega-3s modulate neuroinflammatory pathways, protect neuronal integrity, and support neurogenesis when delivered via nanosponges. Through a comparative analysis of conventional versus nanosponge-mediated delivery systems, the review underscores the superiority of CD-NS in overcoming pharmacokinetic barriers. Preclinical evidence and recent in vivo studies are highlighted to validate the neurotherapeutic efficacy of this nanotechnology-based delivery approach. By bridging the gap between nutraceutical science and nanomedicine, this review aims to inspire students, researchers, and pharmaceutical innovators to further investigate cyclodextrin nanosponges as a promising frontier in targeted therapy for neurodegenerative diseases. The integration of bioactive lipids and smart nanocarriers could redefine the landscape of CNS drug delivery.

Keywords
Docosahexaenoic Acid, Eicosapentaenoic Acid, Neuroinflammation, Nanocarriers, Nanosponges, etc.

I. Introduction
Essential fatty acids known as omega-3 polyunsaturated fatty acids (PUFAs) are mostly found in food or supplements. DHA and EPA, which have been extensively researched for their neuroprotective, anti-inflammatory, and antioxidant qualities, are particularly abundant in marine oils. Synaptic plasticity, receptor function, and membrane fluidity are all impacted by DHA, a significant structural lipid component of neuronal membranes in the central nervous system. Numerous preclinical and clinical studies have linked omega-3 supplementation to decreased neuroinflammation, slower cognitive decline, and altered neurodegenerative pathways linked to various illnesses. *(Ali & Chen, 2015)*

According to recent research, omega-3 fatty acids provide neuroprotection against oxidative stress-induced apoptosis in neuronal cells by balancing the production of neurotrophic factors (such as BDNF) and controlling inflammatory mediators via the NF-κB and Nrf2/ARE pathways. Furthermore, DHA has demonstrated improvements in mitochondrial function and autophagic flux, two important aspects of neurodegenerative disease.

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Advanced delivery systems such as cyclodextrin-based nanosponges (CD-NS) have emerged as promising nanocarriers capable of overcoming solubility and stability issues, while also enabling targeted and sustained release of therapeutic agents. *(Ali & Chen, 2015)*

The practical use of omega-3 fatty acids is severely hampered by a number of formulation and pharmacokinetic issues, despite the compounds' broad therapeutic potential in the treatment of neurodegenerative disorders. The main obstacles preventing them from becoming as successful as they may be including chemical instability, poor water solubility, and limited systemic absorption. One of the most significant issues is the chemical instability of omega-3 polyunsaturated fatty acids (PUFAs), which is due to the existence of many unsaturated double bonds in their structure. These double linkages make omega-3 fatty acids extremely vulnerable to oxidative breakdown, resulting in the generation of lipid peroxides. Not only does this oxidative breakdown reduce the therapeutic efficacy of the fatty acids, but it can also produce cytotoxic byproducts that may further compromise cellular health. *(Ando et al., 2018)*

In addition, omega-3 fatty acids exhibit poor aqueous solubility due to their lipophilic nature. This poses a major obstacle in pharmaceutical formulation, particularly for oral and intravenous routes of administration, where efficient dispersion and absorption in the aqueous physiological environment are necessary. The inability to dissolve effectively in water-based biological fluids results in limited absorption and uneven distribution throughout the body. *(Ando et al., 2018)*

Significant first-pass metabolism limits the bioavailability of omega-3 fatty acids when they are taken orally. Before entering the systemic circulation, the liver processes a substantial portion of the ingested dosage, leaving just a small portion accessible for therapeutic effect. The absorbed portion is particularly needed in the brain for treating neurodegenerative illnesses, however it is not effectively delivered since site-specific targeting is lacking. The breakdown of omega-3 PUFAs in the gastrointestinal system exacerbates these issues. Enzymatic hydrolysis and micellar dispersion activities that occur during digestion further weaken the structural integrity of these fatty acids and decrease their total absorption. Preserving the bioactivity of omega-3 fatty acids requires developing methods to protect them from the hostile gastrointestinal environment. *(Barichello et al., 2019)*

Exploring and implementing cutting-edge delivery technologies that can solve the solubility, stability, and targeting restrictions associated with omega-3 fatty acids is crucial in light of these complex issues. Particularly for progressive and chronic neurodegenerative illnesses, these state-of-the-art systems can significantly enhance the therapeutic outcomes of omega-3-based therapy. Cyclodextrins (CDs) are cyclic oligosaccharides that, due to their hydrophilic outside and hydrophobic interior cavity, can form inclusion complexes with hydrophobic medications such as omega-3 fatty acids. When crosslinked with suitable agents (such as pyromellitic dianhydride or diphenyl carbonate), they create porous, three-dimensional nanostructures called nanosponges, which have controlled release properties and a high loading capacity. *(Barichello et al., 2019)*

Recent research has shown that β-cyclodextrin-based nanosponges may significantly improve the therapeutic potential of omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). One of the biggest advantages of these nanosponges is their ability to resolve a crucial formulation problem with these lipophilic compounds by increasing the water solubility of DHA and EPA by up to 10 times. Achieving therapeutic quantities in the central nervous system requires improved absorption and bioavailability, which is made possible by this higher solubility. Furthermore, it has been demonstrated that β-cyclodextrin-based nanosponges enhance oxidative stability while being stored. DHA and EPA's highly unsaturated structure makes them vulnerable to quick oxidation, which can cause deterioration and a loss of effectiveness. Encapsulation within the nanosponge matrix provides a protective environment, significantly reducing oxidative degradation over time. *(Gidwani & Vyas, 2015)*

Moreover, these nanocarriers offer protection against enzymatic degradation, which typically limits the bioactivity of omega-3 fatty acids when administered via conventional routes. The inclusion complexation and porous 3D structure of the nanosponges act as a shield, allowing the fatty acids to reach their target site intact. Perhaps most compelling is their ability to enable sustained and targeted release, particularly at sites of neuroinflammation. The smart release behavior of nanosponges—triggered by specific pH or enzymatic conditions—ensures that DHA and EPA are released in a controlled manner, directly at inflamed or diseased neuronal regions. *(Gidwani & Vyas, 2015)*

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For the treatment of chronic neurodegenerative illnesses, β-cyclodextrin-based nanosponges are a promising delivery strategy because of their customized administration, which lowers systemic side effects and enhances therapeutic outcomes. CD-NS can be coated with polysorbate 80 or functionalized with certain ligands (such glutathione, lactoferrin, or transferrin) to promote receptor-mediated transcytosis across the blood-brain barrier. Studies on Alzheimer's and Parkinson's disease in mice have demonstrated that this functionalization improves the effectiveness of omega-3 PUFAs in targeting the brain.

Role of Omega-3 Fatty Acids in neurodegenerative diseases

The characteristic of a broad category of chronic, progressive illnesses known as neurodegenerative diseases (NDs) is the gradual degradation of the structure and function of the central or peripheral nervous systems. Huntington's disease (HD), Parkinson's disease (PD), Alzheimer's disease, multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) are a few of these illnesses. With an aging population, neurological illnesses are becoming more prevalent worldwide, putting tremendous strain on caregivers and healthcare systems. *(Güngör, Erdal, & Aksu, 2013)*

Pathophysiology of major neurodegenerative diseases

Alzheimer's Disease (AD)

The characteristics of AD are memory loss, aberrant behavior, and progressive cognitive deterioration. Neuronal death, intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, synaptic dysfunction, and extracellular amyloid-beta (Aβ) plaques are all pathologically linked to it. Furthermore, neuroinflammation, mitochondrial dysfunction, and oxidative stress all significantly influence its development.

Parkinson's Disease (PD)

The main way that Parkinson's disease affects motor function is by causing dopaminergic neurons in the substantia nigra pars compacta to die. One feature is intracellular clumps of α-synuclein, which are commonly referred to as Lewy bodies. Depression and cognitive decline are examples of nonmotor symptoms that are also prevalent. Neuroinflammation, mitochondrial dysfunction, and oxidative stress all affect the course of disease.

Amyotrophic Lateral Sclerosis (ALS)

Upper and lower motor neuron degeneration, which causes muscle weakness, atrophy, and ultimately paralysis, is a hallmark of ALS. Although the precise cause is yet unknown, several variables are implicated, including protein aggregation, oxidative stress, glutamate excitotoxicity, and mitochondrial dysfunction. Neuroinflammation & genetic mutations (e.g., SOD1, C9orf72) also play roles.

- ***Mechanistic insights in neurodegenerative disease***

Progressive neuronal loss and compromised synaptic function are hallmarks of neurodegenerative illnesses. The root reasons are complex and include excitotoxicity, mitochondrial dysfunction, oxidative stress, chronic neuroinflammation, and protein misfolding. A accumulation of toxic proteins damages neurons by activating microglia and generating pro-inflammatory cytokines. Mitochondrial dysfunction causes ATP depletion and excessive ROS generation, which increases cellular stress. Glutamate-induced excitotoxicity and disturbance of calcium homeostasis have a stronger effect on neuronal death. Additionally, neuroinflammation and a lack of neuroprotection are caused by the blood-brain barrier breaking down. New research also links genetic abnormalities and compromised autophagy to the development of the illness. Finding treatment targets requires an understanding of these interrelated molecular mechanisms. By modifying these important processes, omega-3 fatty acids have the potential to provide neuroprotection. This is especially true when they are efficiently transported to the brain using cutting-edge nanocarriers. It exhibit several neuroprotective mechanisms:

- **Anti-inflammatory Effects**: By inhibiting astrocyte and microglia activation, omega-3 fatty acids lower neuroinflammation. Pro-inflammatory cytokine production is reduced by encouraging the synthesis of anti-inflammatory mediators including resolvins and neuroprotectin D1.
- **Neuroprotective Actions**: By modifying apoptotic pathways, lowering oxidative stress, and enhancing mitochondrial function, DHA and EPA increase neuronal survival. Additionally, they promote synaptic plasticity and neuronal growth by upregulating neurotrophic factors including brain-derived neurotrophic factor (BDNF).
- **Membrane-Stabilizing Properties**: As integral components of neuronal membranes, omega-3s maintain membrane fluidity, facilitating efficient neurotransmission. They influence membrane-bound receptor function and ion channel activity, crucial for neuronal signaling.

Omega-3 fatty acids exhibit multifaceted neuroprotective properties, including anti-

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inflammatory, antioxidative, and membrane-stabilizing effects. While preclinical studies are promising, clinical trials have produced variable outcomes, highlighting the need for further research to elucidate their therapeutic potential in neurodegenerative diseases.

Cyclodextrin-Based Nanosponges & its properties

In drug delivery systems, CD-NSs (cyclodextrin-based nanosponges) are gaining popularity as versatile nanocarriers, particularly for the targeted distribution of bioactive compounds like omega-3 fatty acids. They are appropriate for use in the treatment of neurodegenerative illnesses due to their distinct structural and physicochemical characteristics. *(Hu, Fang et al. 2013)*

Structural Overview of Nanosponges using Cross-Linked Cyclodextrin Polymers

CD-NSs are three-dimensional, cross-linked polymeric networks formed by the polymerization of cyclodextrin monomers with suitable cross-linking agents. Because of the large surface area and porous structure created by this cross-linking, several medicinal substances can be encapsulated. By using the right cross-linkers and regulating the degree of cross-linking, the porosity and surface area of CD-NSs may be customized. This affects the mesh size and, in turn, the loading capacity and release profile of the pharmaceuticals that are encapsulated. *(Kadian, 2018)*

Synthesis Techniques and Evolution of CD Nanosponges

The synthesis of CD-NSs has evolved through several generations, each introducing new functionalities and improved properties. *(Yadav & Panchory, 2013)*

1. ***First Generation (Plain Nanosponges):*** Cyclodextrins are combined with cross-linkers like epichlorohydrin, diisocyanates, or carbonyl compounds to create these simple nanosponges, which have different levels of porosity and swelling capacity.
2. ***Second Generation (Modified Nanosponges):*** Before or after cross-linking, functional groups are added to give certain characteristics like charge, fluorescence, or targeting capabilities.
3. ***Third Generation (Stimuli-Responsive Nanosponges):*** Controlled medication release in response to particular physiological triggers is made possible by these nanosponges, which react to environmental cues like pH, temperature, or redox conditions.
4. ***Fourth Generation (Molecularly Imprinted Polymers):*** These nanosponges are very selective and especially helpful in targeted medication delivery applications since they are made with precise binding sites for target molecules.

Mechanochemical approaches, solvent-based methods, and hot-melt processes are examples of synthesis techniques. To create nanosponges without the need for solvents, the hot-melt approach, for example, combines cyclodextrins with cross-linkers such as diphenyl carbonate at high temperatures. Ball milling is one method of mechanochemical synthesis that provides a scalable and solvent-free way to produce CD-NSs. *(Bolmal et al., 2013)*

Physicochemical Properties Relevant to Drug Delivery

Particularly for lipophilic substances like Omega-3 fatty acids, cyclodextrin-based nanosponges (CD-NS) are excellent options for targeted drug administration due to their distinct physicochemical characteristics. Their adjustable mesh size is one of their most important characteristics; it can be precisely regulated during synthesis by altering the kind and strength of cross-linking. This enables the prolonged release and selective encapsulation of bioactive compounds. *(Shivani & Poladi, 2015)*

Swelling behavior is another key attribute—nanosponges can swell in aqueous environments without disintegration, facilitating controlled drug diffusion and responsiveness to physiological pH. This property enhances bioavailability and improves mucosal adhesion, especially beneficial for central nervous system targeting. Moreover, CD-NS demonstrate exceptional *stability*, resisting degradation under physiological conditions. Their robust structure safeguards encapsulated drugs from oxidative degradation and enzymatic breakdown, prolonging shelf life and systemic circulation time. Collectively, these features enable efficient, site-specific, and safe delivery of therapeutics in challenging disease environments like the brain. *(Thakre, Gholse, & Kasliwal, 2016)*

The physicochemical properties of CD-NSs are critical for their performance as drug delivery systems:

- **Tunable Mesh Size:** The kind and quantity of cross-linker may be changed to influence the nanosponges' mesh size, which will affect the drug's release rate and encapsulation effectiveness.

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- **Swelling Behavior:** The degree of cross-linking influences CD-NSs' ability to swell. Increased swelling from lower cross-linking densities can improve medication loading and release characteristics.
- **Stability:** CD-NSs are appropriate for a range of drug delivery applications due to their great chemical and thermal stability. Because of their stability, encapsulated medications are shielded from deterioration and can be released gradually over long periods of time.

These properties collectively contribute to the effectiveness of CD-NSs in delivering therapeutic agents like omega-3 fatty acids, offering potential benefits in the treatment of neurodegenerative diseases.

Encapsulation and Targeted Delivery of Omega-3 Fatty Acids

Omega-3 fatty acids have potent antioxidant, anti-inflammatory, and neuroprotective qualities. However, their instability, poor solubility, and inefficient brain targeting limit their therapeutic use. Encapsulation in nanocarrier systems, including cyclodextrin-based nanosponges (CD-NS), provide a viable way to address these issues. The cross-linked, porous structure of CD-NS facilitates the effective encapsulation of lipophilic Omega-3 molecules, improving their solubility and stability. *Rita et al. (2011)* Additionally, receptor-mediated transcytosis across the blood-brain barrier is facilitated by surface modification with targeting ligands, allowing for site-specific delivery to neuronal tissues. Long-lasting therapeutic doses at the target location are guaranteed by controlled release kinetics made possible by nanosponge matrices. In addition to increasing bioavailability, this focused administration strategy reduces systemic adverse effects. Omega-3 encapsulation in CD-NS offers a novel approach to boosting the therapeutic potential of these molecules in the treatment of neurodegenerative illnesses. *Ahmed et al. (2013)*

Encapsulation Strategies Using Cyclodextrin Nanosponges

As carriers for encapsulating omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), cyclodextrin (CD)-based nanosponges have demonstrated considerable promise due to their capacity to form inclusion complexes that enhance stability and control release patterns. For instance, encapsulating fish oil using β-cyclodextrin (β-CD) has demonstrated effectiveness, with an encapsulation efficiency of 84.1% and fish oil loading of 62.7% at a β-CD to fish oil ratio of 10:20 (w/w). This formulation showed decreased fish oil leakage and enhanced oxidative stability during freeze-drying. *Singh et al. (2016)*

The stability of encapsulated omega-3 fatty acids has also been demonstrated to be further improved by coating with whey protein isolate (WPI) and combining β-CD with oleogel structures. After four hours of UV exposure, more than 50% of EPA and DHA were still present in these systems, suggesting strong defense against oxidative deterioration. *Jilsha and Viswanad (2013)*

Comparative Analysis of β-Cyclodextrin–Fish Oil Complexes vs. Other Nanoformulations

The delivery mechanism known as β-Cyclodextrin (β-CD)–fish oil complexes has shown promise in improving the stability and bioavailability of omega-3 fatty acids. The encapsulation of fish oil in the hydrophobic cavity of β-CD provides protection against oxidative degradation, enhances solubility, and covers up offensive smells. In contrast to other nanoformulations like liposomes, solid lipid nanoparticles (SLNs), and nanoemulsions, β-CD complexes are easier to formulate and have better shelf stability without the need for emulsifiers or surfactants. *Shringirishi et al. (2014)*

Although SLNs and liposomes offer superior controlled release and encapsulation efficiency, they are susceptible to physical instability and leakage over time. Despite their effectiveness, nanoemulsions frequently need stabilizers and considerable energy input. On the other hand, β-CD complexes are more economical, biocompatible, and appropriate for use in functional foods and oral applications. In contrast to traditional β-CD complexes and other nanoformulations, β-CD-based nanosponges provide additional improvements for targeted CNS administration by permitting prolonged release and blood-brain barrier penetration. *Kaur et al. (2015)*

When comparing β-CD–fish oil complexes to other nanoformulations like liposomes and emulsions, several distinctions emerge:

- **Liposomes**: For EPA and DHA, liposomes—especially those made with soybean lecithin—have demonstrated encapsulation efficiencies that are almost 100%. However, environmental conditions might affect their stability, and they might need extra antioxidants to stop lipid oxidation.
- **Emulsions**: When compared to conventional encapsulated formulations, emulsified fish oil supplements have shown improved

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absorption rates of omega-3 fatty acids. This is explained by the enhanced ability of pancreatic lipase to break down and absorb emulsified lipids more quickly.

While emulsions may offer greater bioavailability and β-CD complexes offer superior protection against oxidation and odor masking, liposomes may require stabilizing techniques to retain their integrity despite their high encapsulation efficiency.

Effect of Formulation Parameters on Encapsulation and Release

The effectiveness of encapsulation and the release characteristics of omega-3 fatty acids in cyclodextrin-based nanosponges are largely determined by formulation factors. The formation, porosity, and durability of the nanosponge matrix are greatly influenced by a number of factors, including the solvent system, drug-to-polymer ratio, cyclodextrin variation (α, β, or γ), and the kind and degree of cross-linking agent. Due to restricted cavity accessibility, a higher cross-linking density may lessen drug entrapment while increasing structural stiffness. Lower cross-linking, on the other hand, may limit sustained release but enhance encapsulation. *Martins et al. (2007)* The best hydrophobic interactions with Omega-3 molecules are frequently obtained by using β-cyclodextrin, which improves drug loading. Surface charge and particle size also have an impact on cellular absorption and release kinetics; smaller, evenly spaced nanosponges facilitate regulated release and quicker brain penetration. Formulation design is a key component of efficient targeted delivery systems for neurodegenerative diseases as it balances long-term neuroprotection with rapid therapeutic benefits. Formulation parameters significantly influence the encapsulation efficiency and release profiles of omega-3 fatty acids. *Martins et al. (2007)*

- **CD : Oil Ratio**: An optimal β-CD to fish oil ratio of 10:20 (w/w) has been identified, balancing high encapsulation efficiency (84.1%) and fish oil loading (62.7%).
- **Particle Size**: Smaller particle sizes, as seen in liposomal formulations averaging 73.1 nm, correlate with higher encapsulation efficiencies and improved stability due to increased surface area and better protection of encapsulated lipids.
- **Processing Conditions**: When spray drying, the temperature of the air input and the emulsifying temperature have an impact on the stability and viscosity of emulsions, which in turn impacts the encapsulation yield and efficiency. With the following optimal conditions, a 79.6% encapsulation efficiency may be attained: 35% solids concentration, 3:7 oil to barrier material ratio, 55°C emulsifying temperature, and 220°C air inlet temperature.

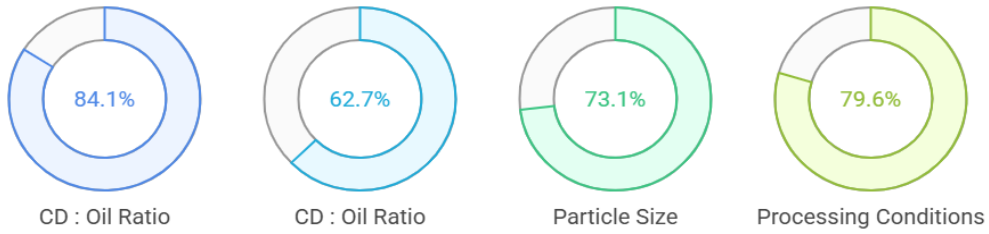

Figure 1. Encapsulation efficiency and dish oil loading

To ensure the stability, controlled release, and bioavailability of omega-3 fatty acids in specific delivery applications, these factors must be meticulously adjusted to get the intended encapsulation results. Particularly those that employ β-CD, cyclodextrin-based nanosponges can be used to encapsulate and deliver omega-3 fatty acids in a targeted manner. The stability, release control, and therapeutic potential of omega-3 fatty acids in the treatment of neurological illnesses can all be improved by customizing these systems through formulation parameter optimization and comparison with other nano formulations. *Naga et al. (2013)*

Mechanisms of Targeted Delivery and Controlled Release

Therapeutic drugs must be delivered exactly at the site of action with a regulated release over time for a drug delivery system to be successful. Promising nano-carriers for omega-3 fatty acids (ω-3 FAs) are cyclodextrin-based nanosponges (CD-NS), which provide improved solubility, degradation resistance, and adjustable release profiles. Their targeted and regulated delivery functions are explained in detail in this section, along with the chemical mechanisms and design techniques that underlie them. *(Neves et al., 2017)*

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Molecular Interactions Between Cyclodextrin Nanosponges and Omega-3 Fatty Acids

Cyclodextrin-based nanosponges (CD-NS) improve encapsulation, stability, and controlled release by interacting with Omega-3 fatty acids via a variety of non-covalent forces. Specifically, the hydrophobic cavities of cyclodextrin units accommodate the long-chain polyunsaturated structure of Omega-3s. The hydroxyl groups on the CD surface and the polar carboxyl groups of Omega-3s form hydrogen bonds and van der Waals forces that improve molecule stability. *(Trotta, 2011)* Omega-3 molecules are trapped in a porous matrix created by cross-linked nanosponge networks, protecting them from oxidation and enzymatic breakdown. Adding targeting ligands to the surface of nanosponges can help make brain-specific delivery even easier. Because of these synergistic chemical interactions, CD-NS provides an efficient nanocarrier platform for neuroprotective therapeutics, greatly enhancing the solubility, bioavailability, and CNS targeting of Omega-3 fatty acids. Made from cyclodextrins, which are cyclic oligosaccharides that are well-known for their capacity to hold hydrophobic molecules in their cavity, cyclodextrin nanosponges are three-dimensional crosslinked polymeric structures. *(Trotta, 2011)*

- **Host–Guest Inclusion Complexation**: The hydrophobic tail of omega-3 fatty acids forms stable inclusion complexes by fitting tightly into the lipophilic cavity of cyclodextrins. Since omega-3 fatty acids are otherwise vulnerable to oxidation and destruction, this improves their solubility and stability.
- **Hydrogen Bonding and Van der Waals Interactions**: A high binding affinity is also influenced by additional molecular interactions, such as hydrogen bonding between the carboxylic groups of ω-3 FAs and the hydroxyl groups of CD, in addition to Van der Waals forces.
- **Entrapment in Nanoporous Matrix**: In addition to being included in cavities, ω-3 FAs are physically confined in the sponge-like polymer network's nanopores, providing dual loading and prolonged retention.

Surface Modification for Site-Specific Targeting

An essential tactic for achieving site-specific targeting is surface modification of cyclodextrin-based nanosponges (CD-NS), especially when it comes to delivering Omega-3 fatty acids to the brain in neurodegenerative diseases. By functionalizing the surface of the nanosponge with ligands like aptamers, antibodies, or peptides (like lactoferrin or transferrin), receptor-mediated endocytosis is made possible across BBB. In the central nervous system, these ligands increase absorption and accumulation by identifying and attaching to overexpressed receptors on brain endothelial cells. *(Francis & Yusuf, 2019)* Additionally, by lowering opsonization and immunological clearance, PEGylation increases the stability and circulation duration of nanosponge. The targeted release of Omega-3s can be regulated by the use of stimuli-responsive moieties, such as linkers that are sensitive to pH or redox. Surface engineering reduces systemic toxicity and off-target effects in addition to facilitating accurate medication administration. Therefore, by facilitating the effective, focused, and long-term distribution of neuroprotective medicines in neurodegenerative illnesses, smart surface modification greatly expands the therapeutic potential of CD-NS. The surface of nanosponges can be altered with specialized targeting ligands to enable site-specific delivery, especially through complex biological barriers such as the blood–brain barrier (BBB).*(Vyas, Saraf, & Saraf, 2008)*

- **Ligand Conjugation:** Ligands that bind to receptors overexpressed on the BBB or disease sites (e.g., inflamed neurons or cancerous tissues) are chemically conjugated onto the surface of nanosponges.
- **PEGylation**: Polyethylene glycol (PEG) is often grafted to provide stealth properties, enhancing circulation time and reducing clearance by the immune system.
- **pH or Enzyme-Responsive Coatings**: Coatings responsive to the acidic microenvironment (like in tumors or inflamed tissues) or specific enzymes can trigger exposure of targeting moieties at the right site.

Controlled and Stimuli-Responsive Release Mechanisms

Cyclodextrin-based nanosponges (CD-NS) provide extremely versatile platforms for stimuli-responsive and regulated drug administration, which is essential for improving treatment results in neurodegenerative illnesses. In order to maintain appropriate therapeutic levels and minimize systemic adverse effects, controlled release guarantees continuous supply of Omega-3 fatty acids over extended periods of time. The porous, cross-linked structure of nanosponges, which controls the drug's distribution and rate of breakdown, makes this possible. *(Zhang et al., 2021)* Through the use of physiological or pathological signals like pH shifts, oxidative stress, or enzymatic activity common in

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neuroinflammatory settings, stimuli-responsive release mechanisms further improve accuracy by initiating medication release. In neurodegenerative lesions, for example, the acidic microenvironment might trigger pH-sensitive nanosponges to release Omega-3s precisely where they are needed. The hallmark of neurodegeneration, excessive oxidative stress, can also be facilitated by redox-responsive connections. These clever delivery techniques greatly enhance medication targeting and lessen side effects, providing a viable method for individualized neurotherapy.

Controlled release of omega-3 fatty acids ensures sustained therapeutic action and minimizes off-target effects. Nanosponges offer both passive and stimuli-triggered release mechanisms.

- ***Diffusion-Controlled Release***

The crosslinked matrix of nanosponges slows the diffusion of ω-3 FAs, enabling prolonged release. The release kinetics are determined by the degree of crosslinking. The diffusion-controlled release mechanism in cyclodextrin-based nanosponges is essential for controlling the long-term release of omega-3 fatty acids (ω-3 FAs). The highly crosslinked three-dimensional polymeric network that makes up these nanosponges has a maze-like structure that traps the drug molecules inside its pores and cavities. *(Roger & Valentine, 1996)*

By directly affecting the matrix's porosity and tortuosity, the degree of crosslinking modifies the pace at which ω-3 FAs diffuse through the polymeric scaffold. A tighter network limits the mobility of entrapped molecules, resulting in a more extended and regulated release profile. As a result, a higher degree of crosslinking usually causes slower drug diffusion. This is especially beneficial for ω-3 FAs, which are quickly metabolized and prone to deterioration when taken in traditional forms. Through the use of diffusion-controlled release via nanosponges, the plasma concentration of ω-3 FAs may be sustained for prolonged periods of time within the therapeutic window, improving bioavailability and guaranteeing steady neuroprotective effects. These controlled release methods also reduce the frequency of doses, enhance patient adherence, and meet pharmacokinetic standards for the treatment of long-term neurodegenerative diseases. *(Elmataeeshy et al. 2018)*

- ***Stimuli-Responsive Systems***

It is possible to build cyclodextrin nanosponges to react to temperature changes (fever or local hyperthermia), enzymes (such as esterase-mediated breakdown), redox conditions (such as high glutathione levels inside cells), and pH variations (such as acidic tumors or inflammatory circumstances). Cyclodextrin nanosponges may be deliberately designed to react to certain physiological or pathological stimuli in the human body because of their adaptable chemical structure and changeable cross-linking networks. Because of their versatility, they are extremely useful for regulated and targeted drug administration, particularly in intricate disease settings like cancer and neuroinflammation.

Among the most promising modifications is the creation of pH-responsive cyclodextrin nanosponges, which are intended to release their therapeutic payload in acidic microenvironments, like those present in tumor locations or inflammatory tissues. The low pH (usually ~5.5–6.5) of sick tissues might stimulate medication release by adding acid-labile linkers to the nanosponge matrix, which will stay stable at normal physiological pH (~7.4). In diseases like cancer and inflammatory brain illnesses, this method is very helpful since it reduces systemic adverse effects while simultaneously improving the treatment's site-specificity. *(Seglie et al., 2011)*

The increased intracellular glutathione (GSH) levels, especially in cancer cells or activated immune cells, are also exploited by redox-responsive nanosponges. These carriers are kept viable in the oxidative extracellular environment by incorporating disulfide bonds into the polymeric structure of the cyclodextrin nanosponges, but they degrade quickly in the reductive intracellular region. This makes it possible for omega-3 fatty acids or other payloads to be released selectively inside cells, improving therapeutic efficacy while preventing needless exposure to healthy tissue.

Enzyme-responsive cyclodextrin nanosponges, which are made to break down in the presence of certain enzymes that are overexpressed in sick situations, including esterases or proteases, provide another clever delivery method. For example, esterases found in inflammatory or malignant tissues can break ester bonds included into the nanosponge network, causing the medicine to be released on-site. When using systemic medicines to treat localized disorders, this enzymatic sensitivity offers a level of biological selectivity that is very desired. *(Williams et al., 2013)*

Lastly, cyclodextrin nanosponges that react to temperature provide an additional level of accuracy in medication administration. These systems are usually made using thermosensitive components that, when exposed to temperature changes, such as fever or localized hyperthermia

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brought on by therapeutic procedures, alter structurally or swell. In areas where the temperature rises over a predetermined threshold, this initiates the controlled release of the encapsulated medication, guaranteeing that drug activation occurs in tandem with the course of the illness or with external therapy cues such as targeted ultrasound or infrared light.

Cyclodextrin-based nanosponges are positioned as next-generation delivery systems that can adjust to the dynamic biological environment thanks to their combined stimuli-responsive characteristics. This makes them especially appropriate for illnesses where traditional delivery techniques are ineffective. When coupled with functional bioactives like omega-3 fatty acids, these smart systems might change targeted treatment for neurodegenerative and inflammatory illnesses.

Advanced application of Nanosponges

The promise of omega-3 fatty acids as a treatment for neurodegenerative diseases is widely known. However, their low water solubility, rapid disintegration, and restricted brain penetration significantly limit their therapeutic effectiveness. In order to address these issues, nanosponge-based drug delivery systems (NSDDS) have become attractive nanocarriers that provide targeted distribution, improved stability, and controlled release, especially to the brain.

Enhancement of Absorption and Protection from Degradation via Nanosponges

Since omega-3 fatty acids are highly unsaturated, they are susceptible to oxidative destruction both in the gastrointestinal system and during storage. Examples of these are EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid). Nanosponges function as molecular "cages" that trap and shield omega-3 molecules from environmental stimuli including light, heat, and oxygen because of their porous three-dimensional network.

Nanosponges based on cyclodextrin have attracted a lot of interest because of their capacity to create inclusion complexes with lipophilic substances like omega-3 fatty acids. While the hydrophilic exterior surface of cyclodextrin guarantees improved compatibility with aqueous conditions, the hydrophobic cavity allows the encapsulation of weakly water-soluble molecules... Omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which generally have poor intestinal absorption and limited water solubility, benefit greatly from this inclusion complex formation. Their apparent solubility and permeability across the intestinal epithelium are greatly increased by adding omega-3s to nanosponges, which eventually improves oral bioavailability and guarantees more reliable therapeutic results. Omega-3 fatty acids are further protected from oxidation by the nanosponge structure, which increases their stability and shelf life in biological systems. *(Selvamuthu Kumar et al. 2012)*

In addition to enhancing solubility, nanosponges made of cyclodextrin are essential for reducing the gastrointestinal tract's enzymatic breakdown of omega-3 fatty acids. Nanosponges' porous and reticulated structure allows them to capture bioactives and provide a regulated, prolonged release over long periods of time. This progressive release approach lowers the frequency of dosing and possible adverse effects linked to peak-dose toxicity, while also assisting in maintaining therapeutic plasma concentrations for extended periods of time. Greater percentages of the supplied dosage are guaranteed to enter the systemic circulation undamaged due to the protection against oxidative degradation and gastrointestinal lipases. For the targeted and effective administration of omega-3 fatty acids in the treatment of chronic neurodegenerative diseases, cyclodextrin-based nanosponges provide an outstanding platform due to their enhanced stability, decreased enzymatic breakdown, and prolonged delivery. *(Shah, Kehinde, & Patel, 2021)*

Recent research has shown that using β-cyclodextrin-based nanosponges to deliver omega-3 fatty acids significantly increases their oral bioavailability when compared to more conventional delivery methods like emulsions. According to study, absorption efficiency can rise by two to three times, indicating that nanosponges have the potential to be better transporters for lipophilic substances. This improvement is mostly due to the high surface area and special porous structure of β-cyclodextrin nanosponges, which enable the creation of stable inclusion complexes with omega-3 fatty acids. For effective absorption, these complexes enhance the solubility of the sensitive fatty acids in aqueous media and shield them from oxidative destruction in the gastrointestinal environment. Additionally, the stable plasma concentration provided by nanosponges' regulated and prolonged release profile eliminates the need for frequent dosage and enhances patient compliance. One other factor contributing to omega-3s' higher pharmacokinetic performance is their enhanced permeability across intestinal

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epithelial cells, which is made possible by nanosponge-mediated encapsulation. As a next-generation strategy for maximizing the therapeutic efficacy of omega-3 fatty acids, especially in situations needing increased neuroprotection, these findings significantly promote the development of formulations based on nanosponge technology. *(Shaikh & Pawar, 2020)*

Improved Brain Uptake and Pharmacokinetic Profiles

Delivering treatments for neurodegenerative diseases still presents one of the most difficult obstacles: getting beyond the blood–brain barrier (BBB). The majority of traditional medications and bioactive substances cannot pass through this strictly controlled barrier, which is intended to safeguard the central nervous system. Because of their variable surface qualities and nanoscale size (~100–200 nm), cyclodextrin-based nanosponges provide a viable way around this restriction. Nanosponges can actively participate in receptor-mediated transcytosis by surface functionalization with targeted ligands like glutathione, lactoferrin, or transferrin. This allows the nanosponges to pass across the blood-brain barrier and ensure effective delivery to brain tissue. These nanocarriers minimize first-pass metabolism by protecting omega-3 fatty acids from enzymatic breakdown and greatly extending their half-life once in systemic circulation. This leads to a significantly increased area under the curve (AUC), which suggests better therapeutic durability and absorption. In a preclinical mouse model, docosahexaenoic acid (DHA)-loaded nanosponges remarkably demonstrated greater targeting ability by achieving up to five times higher brain concentrations than free DHA. In the treatment of Alzheimer's disease and other neurodegenerative diseases, where site-specific action and sustained therapeutic levels are crucial, these results highlight the enormous potential of nanosponge-based delivery systems in enhancing the effectiveness of omega-3 fatty acids. *(Sharma & Pathak, 2011)*

In Vitro and In Vivo Studies Demonstrating Neuroprotective Efficacy

When administered using cyclodextrin-based nanosponges (CD-NS), Omega-3 fatty acids have been shown to exhibit neuroprotective properties in a number of in vitro and in vivo investigations. Comparing Omega-3-loaded CD-NS to free Omega-3s, in vitro tests using neuronal cell lines exposed to oxidative stress or inflammatory cytokines have demonstrated increased cell viability, decreased reactive oxygen species (ROS), and suppressed pro-inflammatory markers (e.g., TNF-α, IL-6). These results imply enhanced anti-inflammatory and antioxidant activities made possible by higher cellular absorption and prolonged release.

Studies conducted in vivo on animal models of neurodegenerative disorders, such as chemically induced Parkinsonian models and transgenic mouse models of Alzheimer's, have shown notable enhancements in neuronal integrity, memory, and motor coordination. Particularly noteworthy were the CD-NS formulations' enhanced blood-brain barrier penetration, extended circulation duration, and specific accumulation in brain tissues. Histopathological evaluations verified decreased amyloid plaque load, gliosis, and neurodegeneration, confirming the therapeutic utility of this delivery method in CNS conditions. *(Subramanian et al. 2012)*

Several preclinical investigations have validated the superior efficacy of nanosponge-based omega-3 formulations in delivering neuroprotective effects:

In Vitro Findings

Comparing omega-3 fatty acid-loaded cyclodextrin-based nanosponges to free omega-3 formulations, recent in vitro studies employing SH-SY5Y neuroblastoma cell lines have demonstrated notable enhancements in cellular absorption. Contributing to this improved internalization are the nanosponges' large surface area, nanoscale size, and capacity to engage with cellular membranes through endocytic pathways. Omega-3s are delivered straight into the cytoplasmic milieu by these internalized nanosponges, where they more effectively exercise their antioxidant qualities. As a result, oxidative stress indicators such nitric oxide (NO), malondialdehyde (MDA), and reactive oxygen species (ROS) are significantly reduced. These results demonstrate the enhanced bioavailability and intracellular delivery potential of nanosponges, which makes them an effective delivery mechanism for oxidative stress management, a major cause of dementia. *(Swaminathan et al., 2010)*

It has also been demonstrated that in neuronal models produced by oxidative stress, omega-3-loaded nanosponges exhibit potent anti-apoptotic properties. When the nanosponge formulation was applied to SH-SY5Y cells subjected to neurotoxic stimuli like glutamate or hydrogen peroxide, it prevented the activation of pro-apoptotic pathways and maintained mitochondrial membrane potential. The expression of caspase-3 and Bax was specifically

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decreased by these nanocarriers, but Bcl-2 was upregulated, suggesting a change toward cell survival and enhanced mitochondrial integrity. Maintaining mitochondrial homeostasis is essential for neuronal survival, and mitochondrial dysfunction is a characteristic of many neurodegenerative disorders, making this significant. These results show strong evidence that cyclodextrin-based nanosponges guard against apoptosis and improve the transport of omega-3 fatty acids, providing a multi-targeted approach to cellular neurodegeneration prevention. *(Dobson, 2008)*

In Vivo Evidence

The neuroprotective effectiveness of cyclodextrin-based nanosponges loaded with omega-3 fatty acids has been well supported by animal research using known models of Parkinson's disease (PD) and Alzheimer's disease (AD). When compared to the administration of free omega-3, these nanosponge formulations showed a notable improvement in neuroinflammatory control and cognitive performance. In particular, pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6 were significantly reduced in treated animals' brain homogenates and cerebrospinal fluid. Alongside this anti-inflammatory profile, there was a discernible reduction in neuronal degeneration, especially in important brain areas including the cortex, substantia nigra, and hippocampus—areas that are frequently impacted in AD and PD. Histopathological examination also showed decreased glial activation and retained neuronal architecture, underscoring the potential of these nanoformulations to slow down neurodegeneration and enhance cellular brain health. *(Szejtli, 1998)*

Concurrently, these findings were functionally validated by behavioral assessments. Memory retention and spatial learning were evaluated using cognitive performance tests, such as the Morris Water Maze (MWM) and the Y-Maze. Mice treated with omega-3 nanosponges showed better working and reference memory in the Y-maze, as seen by increased spontaneous alternation behavior, lower escape latencies, and more time spent in the target quadrant in MWM. Additionally, these mice consistently outperformed the control and free omega-3-treated groups. Together, these behavioral enhancements and the biochemical and histological findings imply that omega-3s delivered by nanosponge improves bioavailability and increases therapeutic effects in models of neurodegenerative diseases. Such findings reinforce the translational potential of this nanoformulation approach in developing effective treatments for cognitive decline and neuroinflammation in PD and AD. *(Szejtli, 1998)*

A recent preclinical study demonstrated the superior neuroprotective efficacy of EPA-DHA-loaded nanosponges compared to free omega-3 fatty acids. In this study, mice given EPA-DHA encapsulated in cyclodextrin-based nanosponges demonstrated a 60% increase in the hippocampal region's antioxidant enzyme activity, specifically SOD and catalase. These enzymes play a critical role in reducing oxidative stress and neutralizing ROS, which are key factors in neuronal damage in neurodegenerative disorders. In contrast to the quickly digested free form, the increased enzymatic activity in the group treated with nanosponge indicates improved stability, prolonged release, and targeted distribution of omega-3 fatty acids to brain regions. Additionally, the porous nanosponge shape enhanced blood–brain barrier penetration and extended circulation. These results highlight the therapeutic potential of nanosponge-based delivery methods in enhancing endogenous antioxidant defense mechanisms, providing a more efficient means of addressing oxidative damage linked to neurodegeneration and cognitive decline. *(Tang et al., 2006)*

A revolutionary strategy for improving the therapeutic profile of omega-3 fatty acids is the use of delivery devices based on nanosponge technology. They provide new opportunities for the treatment of chronic neuroinflammatory and neurodegenerative illnesses by enhancing absorption, preventing degradation, maximizing brain uptake, and exhibiting established neuroprotective benefits in preclinical models. They are positioned as intelligent carriers for next-generation brain-targeted therapeutics due to their multifunctional characteristics.

Therapeutic Potential and Translational Perspectives

A new technique for increasing the brain-targeted distribution and bioavailability of omega-3 fatty acids, namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), is the use of cyclodextrin-based nanosponges (CD-NS). In conditions like multiple sclerosis (MS), Parkinson's disease (PD), and Alzheimer's disease (AD), these essential fatty acids are necessary for maintaining the integrity of neuronal membranes and controlling neuroinflammatory cascades.

Preclinical studies on the delivery of omega-3 fatty acids using cyclodextrin-based nanosponges (CD-NS) have yielded encouraging results,

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particularly when taking neurodegenerative diseases like AD and PD into account. According to research employing transgenic mice models of AD, omega-3-loaded CD nanosponges have a remarkable capacity to cross the blood-brain barrier more effectively than traditional formulations. This is mostly because of their surface functionalization and nanoscale size, which enable both passive and active trafficking across the BBB. Once within the brain, these nanosponges significantly reduce the formation of plaque and the aggregation of amyloid-beta (Aβ), two significant pathogenic indicators of the advancement of AD. Also, they have a strong anti-inflammatory impact by inhibiting pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which are often elevated in neuroinflammatory illnesses. *(Tejashri et al. 2013)*

These preclinical models have shown promise for both neuroprotection and neurorestoration, as seen by the notable increase in synaptic plasticity and cognitive performance. To illustrate the therapeutic superiority of the nanosponge delivery system, in a rat model of Parkinson's disease (PD), docosahexaenoic acid (DHA) formulated in nanosponges not only restored depleted dopamine levels in the striatum but also enhanced motor coordination and behavioral performance more effectively than free DHA.

On the clinical front, there is increasing interest in converting these discoveries into human trials, even if research is still in its early phases. Nanosponge-based omega-3 formulations are being investigated in initial-phase clinical research for their potential to improve oral bioavailability and extend systemic circulation time, two important pharmacokinetic issues that restrict the efficacy of traditional omega-3 supplements. In addition to improving gastrointestinal absorption and providing protection against oxidative degradation, encapsulation inside CD-NS may result in increased plasma concentrations and longer-lasting transport to the central nervous system. In contrast to conventional emulsions or soft gel capsules, CD-NS encapsulation could be a next-generation oral delivery system that is more compatible with patient compliance and therapeutic efficacy. These developments have the potential to redefine omega-3s' function in the treatment of neurodegenerative diseases as the field develops. *(Pushpalatha et al. 2018)*

Regulatory Considerations and future prospective

In both acute and long-term exposure scenarios, cyclodextrin-based nanosponges (CD-NS) have shown a great safety profile with no indications of toxicity or immunogenicity. They decompose into non-toxic byproducts with little chance of systemic accumulation thanks to their biodegradable and biocompatible polymeric matrix, which is crucial for long-term therapeutic applications. One important factor for omega-3 fatty acid treatments, where preserving lipid homeostasis is essential, is that CD-NS do not disrupt endogenous lipid metabolism like many other carriers do. Because of their non-disruptive nature, they are especially well-suited for long-term administration in neurodegenerative diseases, where frequent and extended dosage is frequently required.

Regulators are still working to approve CD nanosponges for use in human treatments, despite these encouraging characteristics. Standardization, scalability, and long-term safety are currently being assessed by organizations like the FDA and EMA, especially in situations involving repeated dosage. When synthesizing nanoparticles, consistency is crucial since batch-to-batch changes can have a big influence on safety and efficacy. Important for commercial translation, regulatory agencies also look for thorough instructions on stability profiles, storage settings, and excipient interactions. Positively, a regulatory avenue for nanosponges is being progressively paved by the rising number of authorized nanocarrier systems, such as liposomes and lipid nanoparticles, which increases the likelihood of their eventual clinical acceptability.

The development of nanosponges is moving in the direction of more intelligent and multipurpose designs in the future. Recent developments include co-delivery systems that mix omega-3 fatty acids with complementary substances like anti-inflammatory medications or antioxidants, as well as stimuli-responsive nanosponges that release their cargo in reaction to particular triggers (temperature, pH, or enzymes). Precision targeting in complicated neurodegenerative diseases is made possible by these multifunctional techniques, which also improve therapy results. Incorporating individualized nanomedicine techniques based on disease-specific and genetic profiles also presents the possibility of customized treatment plans that guarantee optimal effectiveness with few adverse effects. CD-NS are positioned to have a revolutionary impact on next-generation neurotherapeutics as research advances.

II. Conclusion

Cyclodextrin-based nanosponges offer a unique and promising approach to the treatment and prevention of neurodegenerative disorders by delivering omega-3 fatty acids precisely. Because of

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the special structural properties of cyclodextrin nanosponges, such as their high drug-loading capacity, variable porosity, and capacity to form stable inclusion complexes, omega-3 fatty acids can be more soluble, stable, and bioavailable. These carriers not only improve the effectiveness of treatment but also offer site-specific, regulated administration, particularly over difficult biological barriers like the blood–brain barrier. The anti-inflammatory, antioxidant, and neuroprotective properties of omega-3s when administered via nanosponges are confirmed by preclinical research and mechanistic understandings, underscoring the complementary advantages of integrating nanotechnology and nutraceutical treatment. Future studies must concentrate on in vivo validations, long-term safety evaluations, and scaling up production methods in accordance with GMP guidelines in order to turn this promise into clinical reality. A state-of-the-art, multipurpose platform for brain-targeted nutraceutical delivery is cyclodextrin-based nanosponges. Their incorporation into neurodegenerative disease treatment paradigms may lead to safer, more individualized, and more effective neurotherapies, creating intriguing opportunities for both next-generation formulators and pharmaceutical researchers.

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