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# Natural compound loaded nanoparticles for effective treatment of Alzheimer's disease- A review

**Yella Reddy Challa, V. Senthil, N. Jawahar, Raju Bairi**

Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, Tamil Nadu, India - 643001.

Department of Pharmacology, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, Tamil Nadu, India- 643001.

Dr. V. Senthil, Professor, Department of Pharmaceutics JSS College of Pharmacy, Ooty JSS Academy of Higher Education & Research.

**ABSTRACT**

Alzheimer's disease (AD) is the current global challenge in the health care system. Pathophysiological studies revealed that histopathologic lesions are β-amyloid plaques and the neurofibrillary tangles are the primary cause of the AD that are adamant to decompose and accumulate in the brain to cause neurotoxicity. The current treatment is to balance the neurotransmitter levels in the brain at synapse either through acetylcholinesterase inhibitors such as Donepezil, galantamine, and rivastigmine or through Non-competitive N-methyl-D-aspartate (NMDA) receptor antagonists such as memantine. On the other hand, various traditional and Plant-based strategy is also gaining importance nowadays to combat this AD and associated dementia. New drug delivery systems such as Nanotechnology-based approaches like nanosuspensions, nanoparticles, nano emulsions, etc are effective in the management of AD. This review focus on the various natural products and nanotechnological approaches that are established for AD and memory impairment.

**Keywords:** Alzheimer's disease, Nanotechnology, natural products, Plant-based medicine, nanoparticles.

## INTRODUCTION:

Dr. Alois Alzheimer is the first person to illustrate this progressive neurodegenerative disease that targets geriatrics. Alzheimer's disease (AD) is the major cause of more than 80 percent of dementia in elders [1]. Alzheimer's disease is a challenge to the 21st century- the main cause of dementia. More than four crores (40 million) patients are suffering from dementia around the globe, and the number may double by 2040 [2]. Alzheimer's disease is a deadly central nervous system (CNS) neurodegenerative illness that causes memory and cognitive impairment, as well as disorientation, anxiety, language difficulty, and mood changes.

The key histopathological processes found in the pathophysiology of AD are the formation ofextracel lular amyloid plaques in brain atrophy and the association with intracellular tau neuro fibrillary tangles in grey matter loss [3]. β-secretase (BACE1) and γ-secretase cleavages amyloid precursor protein, produces amyloid plaques such as Aβ38, Aβ40, and Aβ42: resistance to proteolysis make it insoluble. The amyloid cascade that involves oxidation, local inflammation, excitotoxicity, and tau hyperphosphorylation triggers the generation of amyloid oligomers-causes the neurotoxicity. A protein makes up the majority of the cortical plaques in Alzheimer's disease brains. The parent protein, APP, is processed to create Aβ.

On chromosome 21, the APP gene is found [4]. The amyloid cascade hypothesis proposed that altered APP processing drove Aβ production, Aβ gave rise to plaques, plaques caused neurodegeneration, which resulted in the clinical dementia syndrome seen in Alzheimer's disease [5,6]. Mutations in two other genes, presenilin 1 on chromosome 14 and presenilin 2 on chromosome 1, have also been linked to early-onset, autosomal dominant AD variations [7,8]. Presenilin mutations increased the production of the 42-amino-acid APP C-terminal degradation product (Aβ42) at the expense of the 40-amino-acid APP C-terminal degradation product (Aβ40) [9].

Enzymes are capable of cutting APP in several places near its C-terminal end. One group of enzymes called α-secretases cut APP 83 amino acids from its carboxyl terminus. Enzymes with α-secretase activity include ADAM ("A Disintegrin and Metalloproteinase") protease family. β-secretase enzymes consist of at least two different complexes named BACE1 and BACE2. The BACE enzymes cut APP 99

amino acids from the carboxyl terminus. The γ -secretase enzyme complex produces the third form of APP cut. γ-secretase's catalytic activity is mediated by presenilin 1 or presenilin 2. APP is cleaved twice by the γ -secretase enzyme. 50 amino acids from the APP carboxyl terminus, one of these cuts occurs. This results in a 50-amino-acid peptide made up of the extreme APP C-terminal end, known as the amyloid intracellular domain (AICD). The location of the other γ -secretase cut varies, although it usually occurs 57, 59, or 61 amino acids from the APP C-terminus.

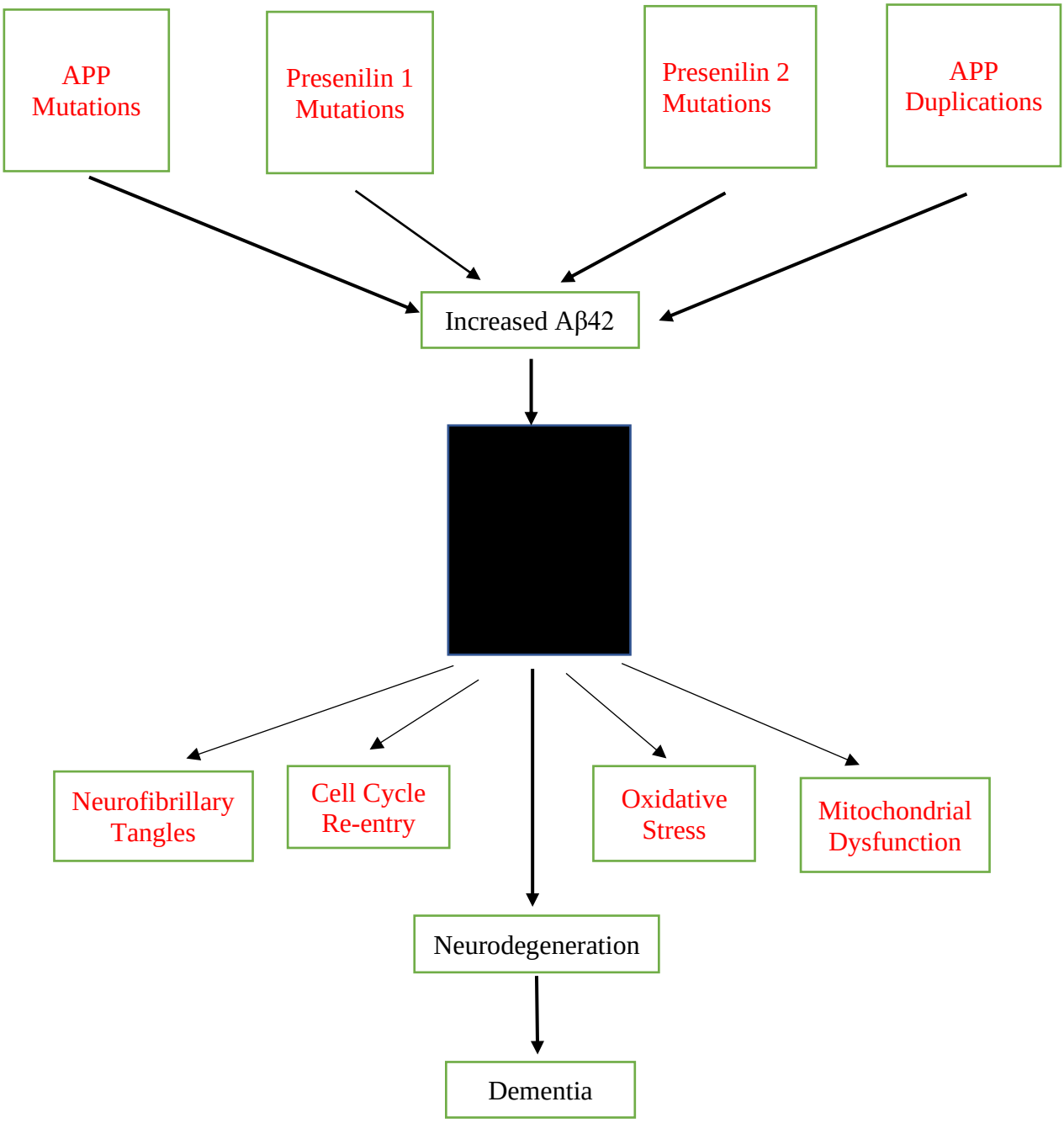


**Figure 1: The amyloid cascade hypothesis. A black box is shown in the middle of figure. Since mechanisms through which drives downstream pathology are not well defined.**

The APP secretases work in combination. Sequential processing by the α and γ-secretase results in a large N-terminal peptide called soluble APPα (sAPPα) and a smaller 3 kD peptide called P3. Proteolysis by enzymes with α-secretase activity precludes sequential β-γ secretase activity. When both the β and γ secretases process APP, the β-secretase cut produces a large N-terminal peptide called soluble APPβ

(sAPPβ), as well as a smaller C-terminal fragment called CTFβ. The γ-secretase cuts CTFβ, and the more upstream (from the APP carboxyl terminus) 4 kD peptide defined by the γ and β secretases is the Aβ peptide. With sequential β-γ secretase activity, the exact γ secretase cut site varies, yielding an Aβ peptide which is typically 38–43 amino acids.

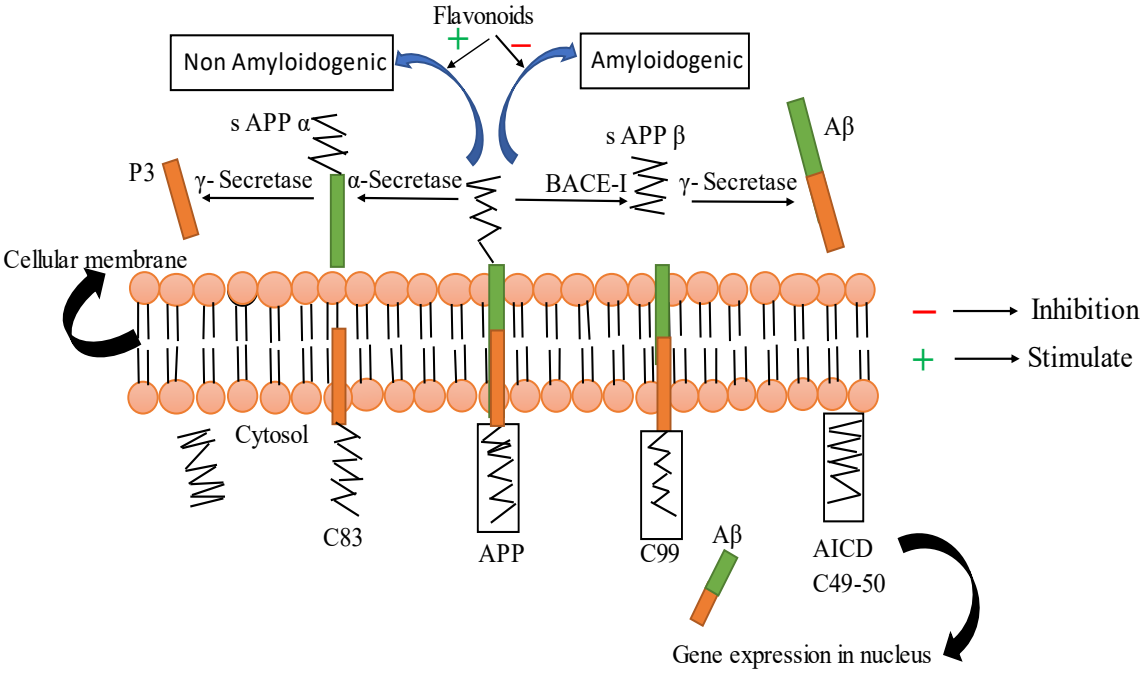


**Figure 2: Flavonoids are thought to activate the non-amyloidogenic pathway by stimulating the activities of α, γ-secretases, while inhibiting the neurotoxic amyloidogenic pathway by blocking the BACE-I enzyme[10].**

Similarly, Abnormal hyperphosphorylation of tau proteins accumulates as Intra neuronic tangles lead to inhibition of microtubule assembly-a necessary step in neuronal development and function. All these events together involved in the evolution of neurotransmitter imbalance (seen in AD) [11,12,13]. Mechanisms involved in the pathogenesis are mutations in amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin 2 (PS2) genes[14].

The clinical manifestation of progressive loss of interneurons of the cortex and biochemical pathways associated with acetylcholine (ACh), noradrenaline (NA), and serotonin (5-HT) can be medicated by balancing the neurotransmitters using acetylcholinesterase inhibitors like donepezil, galantamine, and rivastigmine are the current approach to treat AD that is believed to improve the cognition and memory. Drugs like memantine are also proved effective in balancing the glutamate levels[15]. The three stages of AD include: degeneration of hippocampus in early-stage- causes mild forgetfulness; atrophy of the cortex in moderate stage- causes devaluation of language, the downturn of emotional control, worsening of routine personal tasks and lack of clear thinking; severe degradation of neurons in an advanced stage- forgets the faces[16]. Anti-Aβ agents were effective in the early stages in the clearance of amyloid plaques but, failed to recover the patients of the moderate and advanced stage due to irreversible synaptic loss and neuronal deaths[17].

Currently, various ligands for the management of Alzheimer's disease were gaining importance viz., Ach esterase inhibitors, antioxidants, anti-inflammatory, and neuroprotective compounds.

**Natural compounds reported for Alzheimer's disease**

Plenty of natural compounds were reported to have the potential to manage Alzheimer's disease with multiple mechanisms (**Table1**). Since the natural compounds are having multiple targets, the exact mechanism involved in the anti-Alzheimer's activity is largely unknown.

**Table 1. Natural bioactive compounds for Alzheimer's disease**

| S. No. | Compound name | Mechanism |
|---|---|---|
| 1. | Vitamin D | Reduction of Aβ Level[18] |
| 2. | Vitamin E & C | Reduction of oxidative stress[19] |
| 3. | Homotaurine | Improvement of the central cholinergic transmission[20] |
| 4. | Huperzine A | Reversible che-I[21] |
| 5. | Bryostatin | Activator of protein kinase C epsilon[22] |
| 6. | Melatonin | Antioxidant and anti-amyloid properties[23] |
| 7. | Resveratrol | Activator of sirtuins1[24] |
| 8. | Nicotine | Reduction of Amyloid plaques[25] |
| 9. | Curcumin | Decreased Beta-amyloid plaques, delayed degradation of neurons, metal-chelation, anti-inflammatory, antioxidant and decreased microglia formation [26] |
| 10. | Arctigenin | Inhibit Aβ production and clearance [27] |
| 11. | Dihydromyricetin | Up-regulation of AMPK/SIRT1 pathway to inhibit inflammatory responses [28] |
| 12. | Agaropentose | Reduction of oxidative stress [29] |
| 13. | Boswellic acids | Reduction of oxidative stress and anticholinesterase activity [30] |
| 14. | β-Caryophyllene | CB2 agonist that leads to anti-inflammatory and antioxidant effects [31] |
| 15. | Puerarin | Reduction of oxidative stress [32] |
| 16. | Rosmarinic acid | Increases monoamine secretion and subsequent reduction of β-amyloid aggregation [33] |
| 17. | Osmotin | Inhibit Aβ production [34] |
| 18. | Isogarcinol | Reduction of oxidative stress and anti-inflammatory [35] |
| 19. | Parawixin 10 | Delayed degradation of neurons [36] |
| 20. | Physostigmine | Reversible anticholinesterase [37] |
| 21. | Rutaecarpine | Reducing hyperphosphorylation of tau-associated sites [38] |
| 22. | dehydroevodiamine | Antioxidant activity and inhibition of neurotoxicity and intracellular calcium [39] |
| 23. | Turbinatine | Anticholinesterase [40] |
| 24. | Galantamine | Anticholinesterase [41] |
| 25. | Berberine | Anticholinesterase [41] |
| 26. | Naringenin | Mitigation of lipid peroxidation and apoptosis [42] |
| 27. | Ginkgetin | Antioxidant and anti-amyloid properties [43] |
| 28. | Bacoside-A | Anti-amyloid properties [44] |
| 29. | Luteolin | Reducing PS1-APP interaction and Aβ generation [45] |
| 30. | Quercetin | Quercetin-induced Nrf-2 translocation from the cytoplasm to the nucleus [46] |
| 31. | Lunasin | ameliorate Aβ42 mediated neurodegeneration by downregulating JNK signalling [47] |
| 32. | Catechin | Inhibit Aβ production [48] |
| 33. | Platycodin D | Increase synaptogenesis [49] |

**Role of nanotechnology in Alzheimer's treatment**

Attempts have been made in drug delivery systems to improve the therapeutic efficacy of the natural compounds to treat Alzheimer's disease. Transporting the bioactive compounds from the site of administration to the site of action without affecting their physical and chemical behaviours including decomposition in the biological system is very important and can be achieved by various new drug

delivery systems [50]. Nanotechnology led to several milestones in the drug delivery system; nanoparticles are the ones that are extensively useful to make controlled or sustained released dosage forms. Nanoparticles like nanocarriers make the drug more potent and decrease the therapeutic dose and toxicity [51]. In the case of neurological diseases, the blood-brain barrier (BBB) is the toughest barrier for a drug molecule to cross [52].

This can be modified using definite carriers (be expressed at the target site) to the drug molecules to improve their inflow. Carriers like peptides, adaptamers, antibiotics, cationic molecules are reported to increase the therapeutic efficiency through BBB [53].

Various nanotechnological approaches in drug delivery systems were mentioned below.

1. **Nanosuspensions**

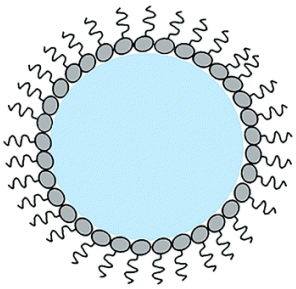

**Figure 3: Structure of Nanosuspension**

A pharmaceutical nanosuspension is a suspension of very finely dispersed solid drug particles in an aqueous vehicle for oral and topical administration, as well as parenteral and pulmonary delivery. Surfactants, polymers, or a combination of both stabilize nanosuspension, which is a sub-micron colloidal dispersion of medicine particles. They can also be defined as a biphasic system that consists of pure drug particles dispersed in an aqueous vehicle with a particle diameter of less than 1um. Nanosuspensions are not the same thing as nanoparticles or solid lipid nanoparticles. Solid lipid nanoparticles are lipid carriers of pharmaceuticals, whereas polymeric colloidal nanoparticles are polymeric colloidal carriers of drugs. The drug is kept in the appropriate crystalline state with a smaller particle size in nanosuspension technology, resulting in a faster dissolving rate and hence higher bioavailability.

2. **Microemulsion**

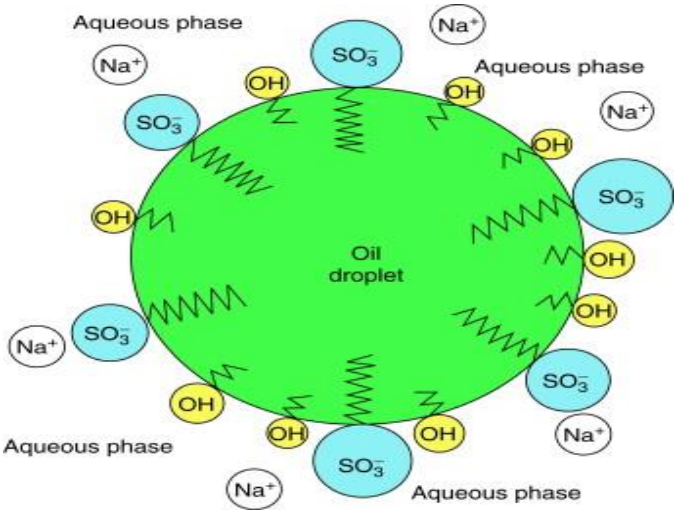


**Figure 4: Diagram of Microemulsion**

Microemulsions are clear, transparent, thermodynamically stable dispersions of oil and water that are stabilized by an interfacial coating of surfactant, which is frequently combined with a co-surfactant [54].

By dispersing oil in an aqueous surfactants solution and adding alcohol as a co-surfactant, the first microemulsion was created, resulting in a transparent, stable formulation.

**3. Nano emulsion**

Nanoemulsions, also known as submicron emulsions, ultrafine emulsions, and mini emulsions, are submicron-sized colloidal particulate systems that are thermodynamically and kinetically stable isotropic dispersions made up of two immiscible liquids, such as water and oil, stabilized by an interfacial film made up of suitable surfactant and co-surfactant to form a single phase.

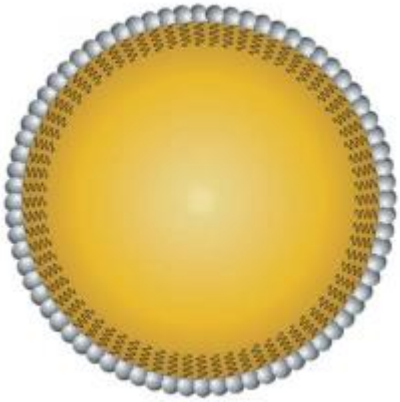

**Figure 5: Structure of Nano emulsion droplet**

Nano emulsions offer various advantages over other dosage forms and these advantages are, (i) increased rate of absorption, (ii) reduced variability in absorption, (iii) protection from oxidation and hydrolysis in O/W nano emulsions, (iv) delivery of lipophilic drugs after solubilization, (v) aqueous dosage form for water-insoluble drugs, (vi) enhanced bioavailability for many drugs, (vii) ability to incorporate both lipophilic and hydrophilic drugs, (viii) delivery systems to enhance efficacy while reducing the total dose and side effects, (ix) as non-toxic and non-irritant vehicles for skin and mucous membrane delivery and (x) release control by permeation of drug through liquid film, whose hydrophilicity or lipophilicity, as well as thickness, can be precise.

**4. Nanocrystals**

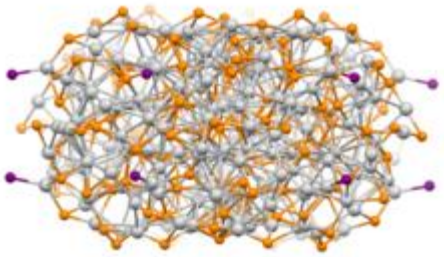

**Figure 6: Diagrammatic representation of Nanocrystals**

Drug nanocrystals were nanometre-scale crystals, meaning crystalline nanoparticles were formed. Availability of drug nanocrystals into fluid materials ends in so-called "nanosuspensions". Typically, the dispersed molecules have to be protected by surfactants or polymeric stabilizers, for instance. An amorphous powder nanoparticle should not be called nanocrystal in the truest sense. Throughout the years, nanoparticles (NPs) derived from organic and inorganic compounds have also been developed to overcome physiological barriers and to provide medicines for a range of indications [55,56]. Water-insoluble or hydrophobic medicines gain financially in order to ensure optimum bioavailability and thus sufficient efficacy [57].

**5. Mesoporous Silica Nanoparticles**

Mesoporous materials having a high specific surface area, pore volume, and distinctive pore size have lately been investigated extensively as bio-materials, such as carriers for regulated delivery of

bioactive principles. In compared to amorphous colloidal silica, mesoporous silica materials have a larger capacity for drug loading and ensure controlled bio-active chemical release if functionalized. Because of their biocompatibility, high loading capacity, ability to attach target ligands for specific cellular recognition, or the design of well-defined and tuneable porosity, mesoporous silica nanoparticles can be used as host materials for transporting therapeutics, medicaments, or encapsulation of molecules [58,59,60.]

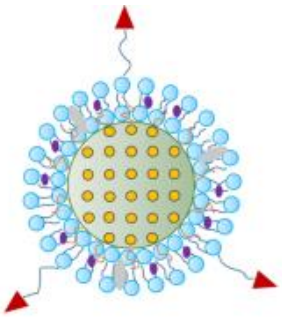

**Figure 7: Schematic representation of Mesoporous Silica Nanoparticles**

**6. Self-Micro Emulsifying Drug Delivery System**

SMEDDS are natural or synthetic oils, stable or liquid surfactants, or one or more hydrophilic solvents and co-solvents/surfactants that may form adequate oil-in-water (o/w) microemulsions after mild agitation and dilution in aqueous media, including GI fluids[61]. These systems were created using a lipid provider that improves the gastro intestinal absorption of poorly water-soluble capsules, allows the drug to stay in the dissolved state by shielding it from enzymatic response, is thermodynamically stable, easy to manufacture, and suitable for oral drug transport [62]. The feature of oil on this system is to solubilize the lipophilic drug to be able to improve the drug loading and bioavailability.

Various delivery systems for the lipophilic drugs are available such as, microemulsion, lipid solution, lipid emulsion, dry emulsion, whose formulation involve large number of possible combination of excipients, further to understand these lipid-based formulation and to get a clear picture of all these different systems a particular classification system have been established called as 'lipid formulation classification system' have been introduced. The classification helps to better understand the fate of different lipid formulation *in vivo* [63].

**STEP A: -**

Solubilizing an insufficiently water-soluble drug, as well as a pharmaceutical ingredient, in a mixture of surfactant and co-surfactant solvents. Currently, integrate the oil stage into the solubilized drug formulation, if necessary, by heat or other preliminary techniques [64].

**STEP B: -**

The emulsion would then be able to be added to a reasonable dosage form, for example, soft or hard-filled gelatine capsule and permitted to cool [65].

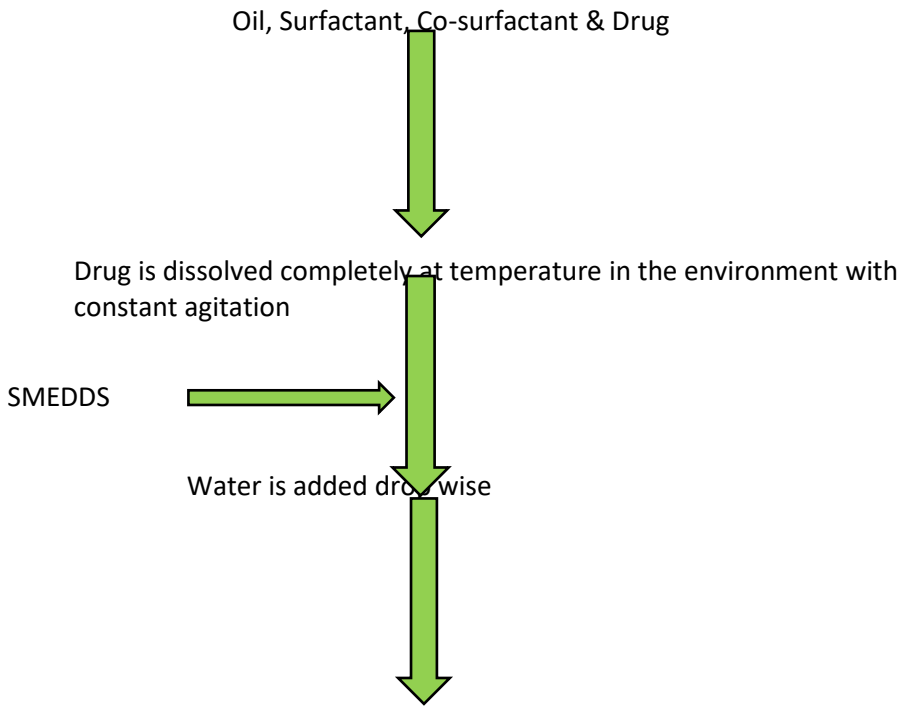


**Figure 8: Flow chart for preparation of SMEDDS [66].**

### 7. Nano Carrier System

In the treatment of neurodegenerative illnesses, nanotechnology in combination with medicines can be employed to overcome numerous difficulties that drug molecules confront. Using nanotechnology-based dosage forms, these features of drug molecules are drastically regulated, and the therapeutic potential of the drug molecules is enhanced using various functional aids [67,68]. Nano formulations address these challenges by securely transporting the drug through the biological milieu with increased permeability, resulting in maximum efficacy at a lower dose. Controlled drug release at the target site is an important property of nanoformulations[69]. The type of the carrier material can be classed as (i) inorganic (gold, carbon, and silica) or (ii) organic for nanosized dosage forms (solid lipid NPs, dendrimers, emulsions, liposomes, and polymers).

Nanosized systems have attracted a lot of attention because of their advantages, such as their capacity to avoid chemical and enzymatic drug degradation, enhance drug solubility, and make drug transport across biological membranes easier. Targeted systems deliver the medicine directly to the place of action, reducing pharmacological side effects and improving the therapeutic index[70]. Nasal mucosal vaccination and medication administration are also possible with nanocarriers. Antigen identification is made possible by nanocarrier systems. The following are subcategories of nanocarrier systems based on their degree of degradability.

The following properties must be included in an ideal nanoparticulate drug delivery system: (1) Maximum drug bioavailability.

(2) Tissue selection.

(3) Kinetics of release that is controlled.

(4) The immunological reaction is kept to a bare minimum.

(5) The ability to administer medications that are typically difficult to distribute, such as lipophiles, amphiphiles, and biomolecules.

(6) Adequate drug loading capability.

(7) A high level of patient compliance.

**i) Solid lipid nanoparticles (SLN)**

SLNs are typically spherical, with a diameter ranging from 50 to 1000 nm. Lipids, which are solid at room temperature, emulsifiers, and sometimes a combination of both, active pharmaceutical ingredients (APIs), and an appropriate solvent system are all crucial elements in SLN formulations (**Figure 9**).

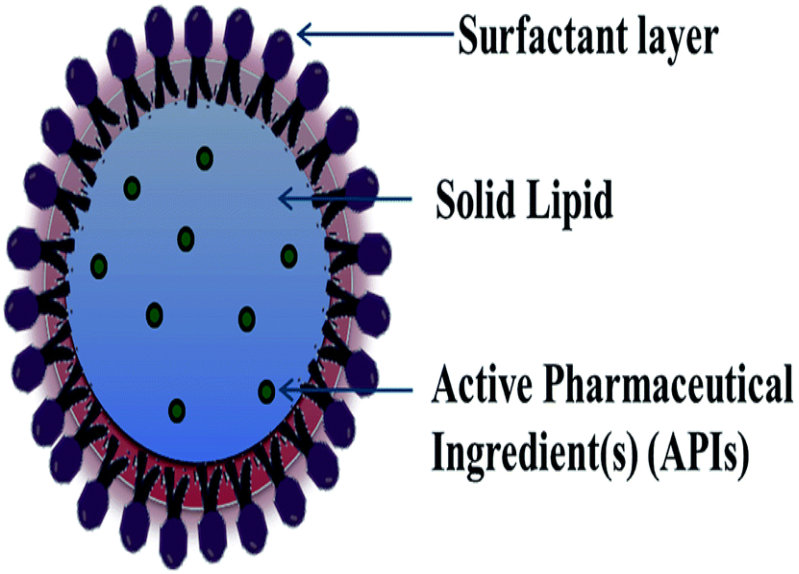


**Figure 9: The full structure of solid lipid nanoparticles is shown schematically**.

**ii) Polymeric nanoparticles**

Polymeric Np is a nanosized carrier (1–1000 nm) composed of natural or synthetic polymers, in which the medication can be loaded in solid or liquid form, or adsorbed or chemically attached to the surface. Polymeric Np is one of the most promising techniques for CNS drug delivery these days [71,72-79]. Np protects implanted pharmaceuticals from chemical or enzymatic degradation, increasing the likelihood that the active molecule will reach the target location. Poly alkyl cyanoacrylate (PACA) [80], one of the most extensively utilized polymers for the manufacture of Np for CNS drug delivery, is currently not approved by the FDA for intravenous administration. FDA-approved polymers such as polylactide-co-glycolide (PLGA) and polylactide (PLA) are two of the most promising polymers for the manufacture of Np. PLA or PLGA is degraded into oligomers and monomers of lactic and glycolic acids (Krebs' cycle substrates) via an autocatalytic cleavage of the ester linkages via spontaneous hydrolysis [81]. These biodegradable polymers have varied periods of elimination from the body depending on their MW and conjugation with other polymers (such as PEG) [81,82]. The Np's tiny diameter correlates to a large relative surface area, which may encourage aggregation. When given, the final size of the Np is a crucial parameter that influences their biological fate in part [83]. Particles smaller than 10 nanometres are quickly evacuated following substantial extravasation and renal clearance, but Np larger than 200 nanometres are swiftly filtrated by the spleen and removed by the reticuloendothelial cells.

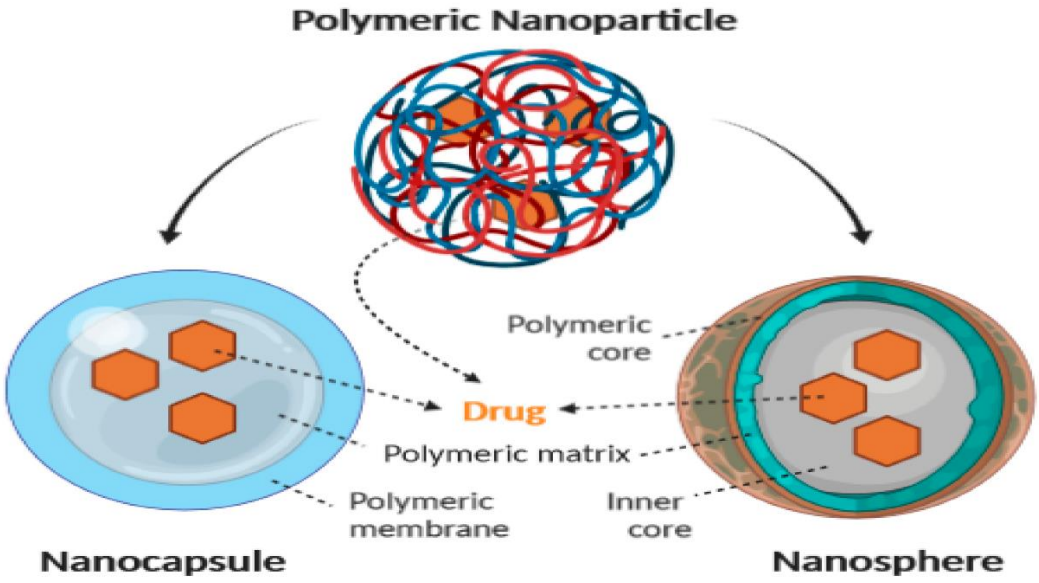


**Figure 10: Preparation of Polymeric nanoparticles**

**iii) Dendrimers**

Dendrimers are three-dimensional polymeric materials composed of repeatedly branched monomeric units called dendrons, which coalesce to form a highly symmetrical structure [84]. The dendrons are single chemically distinct groups attached by chemical bonds to the centre of the dendrimer [85].

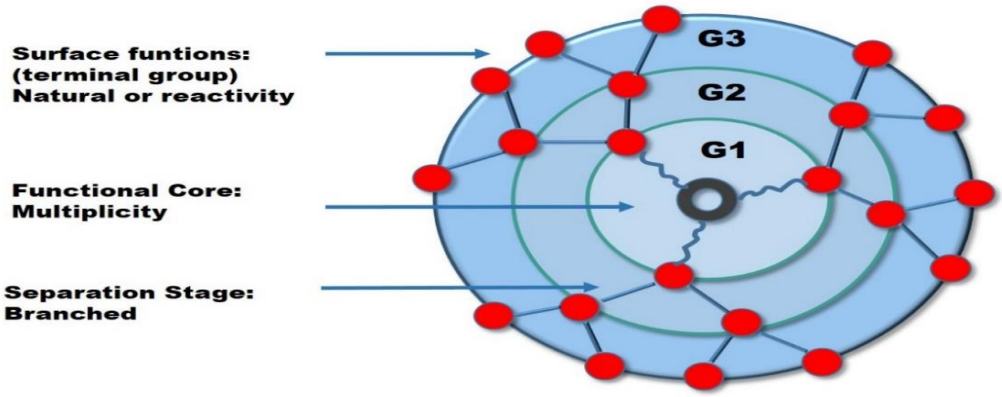


**Figure 11: The basic structure of a dendrimer with three generations**

Dendrimers consist of a central core to which repeated branching cycles, commonly referred to as generations, are added. Each generation is assigned a generation number indicating the number of branching reactions performed onto the core molecule [86]. The ends of these branches form the multivalent surface, which can be specialized for specific functions. Surface functionalization improves the transfection efficiency and the specificity of dendrimers. The increased biocompatibility and controlled release behaviour based on stimuli responsiveness of functionalized dendrimers enhance its therapeutic efficiency [87]. Dendrimers have a multifunctional capability ranging from enhancing solubility, dissolution, gastrointestinal tract (GIT) permeability, stability [88] to promoting better bioavailability, allowing multiple drug entrapment, and controlled delivery [88-91].

There are three main sites for drug entrapment in the dendrimer architecture, which is explained in **table 2**.

**Table 2: Different locations for drug trapping in dendrimers.**

| Site | Mechanism | References |
|---|---|---|
| 1) | Vacant areas Molecule entrapment | [92] |
| 2) | Nodes of departure Hydrogen bonding | [92] |
| 3) | Surface assemblages Interactions between charge with charge | [92] |

**iv) Polymeric micelles**

Micelles are generated by the dispersion of amphiphilic molecules in solution, which contain both hydrophobic and hydrophilic components [93]. Micelles are created through self-assembly, and the process begins only when a specific minimum concentration, known as the critical micellar concentration, is reached. Furthermore, the crucial micellization temperature is the temperature at which amphiphilic molecules form aggregates, and micelles can collapse below this temperature [94]. Polymeric micelles have attracted a lot of attention because of their excellent stability, low cytotoxicity, and appropriateness for regulated and long-term drug delivery. The substantial drug loading capacity of the inner core of polymeric micelles makes them ideal for targeted therapy and long-term drug administration. Hydrophobic contacts, electrostatic interactions, and metal complexation are all examples of mechanisms that can create polymeric micelles [95]. Drug-loaded micelles are mostly made by direct dissolution, solvent evaporation, and dialysis, while polymeric micelles are mostly made by dissolving the block copolymer in a selective/nonselective solvent.

Known amounts of the drug (10 mg) and copolymer (40 mg) were milled in the dry state and then dissolved in dimethylformamide (DMF), a solvent in which both drug and copolymer are soluble. The organic solvent was then vacuum-sealed away, leaving a solid residue. With the addition of aliquots of water (up to 5mL), the copolymer self-assembled into micelle aggregates, allowing drug molecules to be incorporated into the hydrophobic core. The dispersion was then stirred continuously overnight, and the excess medication was removed from the system by filtration through 0.45 m filters, before being freeze-dried. The end result was an 85 percent yield.

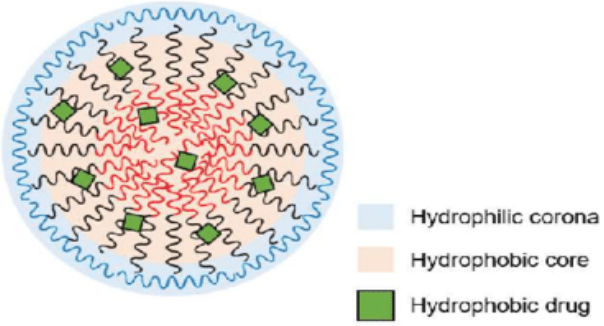


**Figure 12: Diagram of Polymeric Micelle.**

**v) Carbon nanotubes**

Carbon nanotubes (CNTs) are tubular structures made entirely of carbon atoms organized in a sequence of condensed benzene rings. CNT structures are divided into two categories based on the number of layers: single-walled carbon nanotubes (SWCNTs) and multiwalled carbon nanotubes (MWCNTs) (MWCNTs).

SWCNTs are hexagonal close-packed bundles made up of a single graphene cylinder with a diameter ranging from 0.4 to 2 nm.

MWCNTs are built up of two to several coaxial cylinders, each of which is made up of a single graphene sheet encircling a hollow core. MWCNTs have an exterior diameter ranging from 2 to more than 100 nm, an interior diameter of 1–3 nm, and a length ranging from 0.2 to several micrometres [96,97].

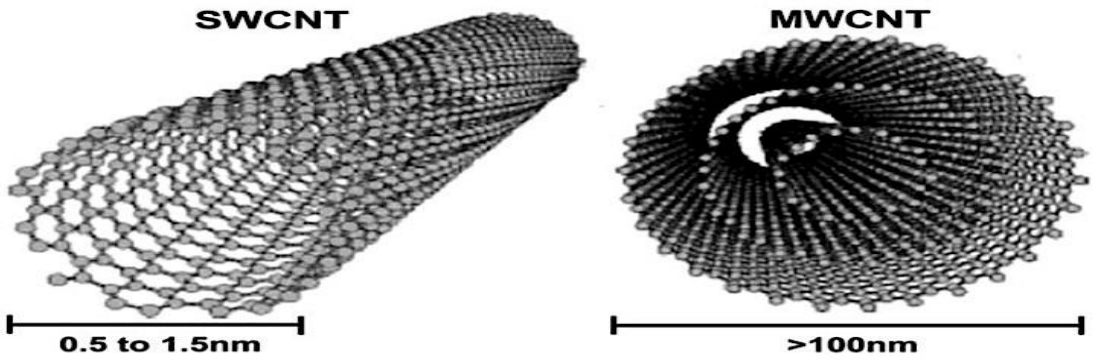


**Figure 13: Structure of Single Wall Carbon Nanotube (SWCNT) and Multi Wall Carbon Nanotube (MWCNT)**

Depending on the direction of the molecule, it can roll in three different ways: armchair, zigzag, or chiral.

CNTs have been employed in neurosciences as a promising biological material [96,98,99,100]. CNTs are able to pass the blood-brain barrier by numerous targeting methods and operate as excellent delivery carriers for the target brain due to their small dimensions and accessible exterior alterations. SWCNTs were successfully employed to transport acetylcholine in mice brains damaged by Alzheimer's disease with a high safety range, according to Yang *et al*, 100. Many other functionalized SWCNTs or MWSCNTs have been effectively employed as delivery vehicles for neurodegenerative illnesses or brain tumours [97,99,101].

**vi) Lipid-Polymer Hybrid Nanoparticles (LPHNP)**

In a water-miscible organic solvent (Acetone, Ethyl alcohol), the drug and polymer were dissolved. In water, lipid/lipid-PEG is dissolved. To achieve a homogeneously dispersed liquid phase, this combination was heated above the gel-to-liquid transition point. Dropwise addition of polymer to the lipid's aqueous phase while stirring continuously. Because of hydrophobic interactions, the polymer coils into nanoparticles with the lipids surrounding it. The inner lipid shell merges with the hydrophobic lipid tails of lipid-PEG.

**8. Vesicular Delivery Systems**

The unique drug delivery system is the most suited and approachable in establishing a delivery system that improves the therapeutic efficacy of new and pre-existing medications, provides controlled and sustained drug delivery to the precise spot, and fulfils the body's genuine and appropriate drug demand. It has the ability to deliver the medicine to a specific site of action. Since then, advances in vesicular drug delivery have led to the creation of systems that enable drug targeting and the prolonged or controlled release of traditional treatments. The major goal is to reduce medication degradation and loss, as well as to reduce severe side effects and enhance drug availability at the illness site.

**i) Liposomes**

Liposomes are spherical organic nanoparticle forms made up of a lipid bilayer encasing an aqueous core and a lipophilic phospholipid layer on the outside (**Figure 14**) [102,103]. The aqueous centre is enclosed to encase water-soluble substances for transportation, ensuring that they arrive at their intended locations [104].

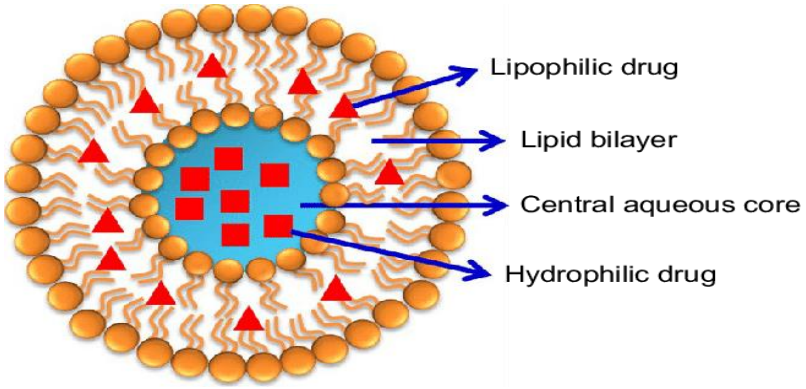


**Figure 14: Diagrammatic representation of Liposome structure.**

The aqueous intermediate allows for the polar segment of the molecule to continue to stay in connection with the polar environment, while still shielding the nonpolar segment. The outer coating surrounding the aqueous centre is made up of fat referred to as a phospholipid bilayer [103,105]. The bilayer phospholipid layer helps transports lipid-soluble agents in the lipophilic layer of the cell membrane (**Figure 14**).

The liposomes can be classified into three groups;

a) Multi Lamellar Vesicles (MLVs)
b) Small Unilamellar Vesicles (SUVs)
c) Large Unilamellar Vesicles (LUVs) [106,107,108].

The MLVs are made up of many lipid layers that are separated by an aqueous solution and are generated spontaneously. MLVs are made by gently shaking them.

The size of small unilamellar vesicles and large unilamellar vesicles is determined by homogenization of MLV with a single lipid layer [109,110]. The phospholipid is made up of a hydrophobic tail (2 fatty acids containing 10- 20 carbon atoms), and a hydrophilic head (phosphoric acid bound to a water-soluble molecule) [103,111]. The lipid can range in size from 25 nm to 5000 nm microscopic fatty material. Therapeutically liposomes can increase a drug's efficacy, stability, control release, administration via multiple routes, targeted tissue action, and assist in the reduction of unnecessary drug toxicity [106,107,111].

Various liposome-based drug delivery systems are studied as a potential treatment for AD.

Oxidative damage is the hallmark of neurogenerative diseases including Alzheimer's disease evidence suggests antioxidants can protect from beta-amyloid toxicity. Curcumin is used as a nutritional supplement. Pharmacologically curcumin has shown antibacterial, anti-cancer, anti-fungal, anti-inflammatory, and anti-Alzheimer properties due to its anti-oxidative properties [112,113,114,115]. It was assumed that nano transporting the substance would improve its solubility. Curcumin loaded into a liposome improves the stability and solubility of the curcumin [113,114]. Curcumin targets Aβ and reduces amyloid plaque formation thereby reducing amyloid-associated toxicity [116]. Curcumin derivative showed high affinity for Aβ42 fibrils and thereby reducing Aβ aggregation and β amyloid plaque formation.

**ii) Niosomes**

Surfactant and cholesterol are mixed together with flowing hydration in water to form noisome structures. The hydrophilic ends of a non-ionic surfactant are exposed on the outside and interior of the vesicle in niosomes, while the hydrophobic chains express each other within the bilayer. Monomer units assemble into vesicles, which form closed bilayer structures, due to strong interfacial tension between water and the hydrophobic tail. Hydrophilic medications are captured within the vesicle's space, while hydrophobic drugs are entrapped within the bilayer itself. Amphiphilic pharmaceuticals have their lipophilicity fixed in the gap between the hydrophilic core and the lipophilic tail.

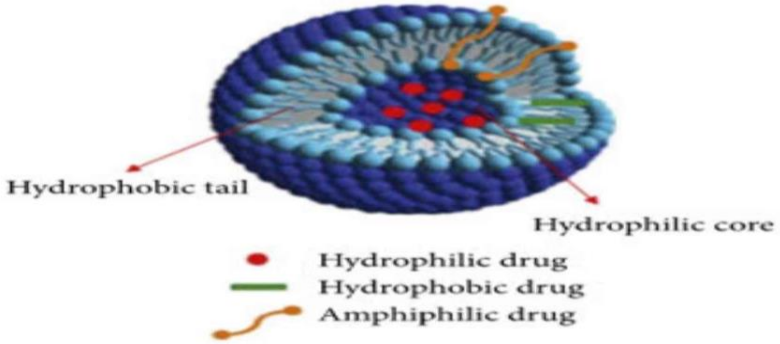


**Figure 15: Schematic representation of Niosomes**

Lipid molecules (cholesterol or L—soya phosphatidylcholine) and non-ionic surfactants are the two main components used in the creation of niosomes. Non-ionic surfactant-based vesicles, also known as niosomes, are drug carriers that require a bilayer structure composed primarily of non-ionic surfactant and lipid molecules integrated into an aqueous phase. Niosomes are grouped into three types depending on three factors: first, the function of niosome size, second, the technique of preparation, and third, vesicle size. For drug targeting to the intended organ/tissue, two types of active targeting techniques are commonly used. One of the ways involved attaching active targeting ligands directly to cholesterol or dedicating ligands to the distal end of PEG chains in PEGylated niosomes. Incorporation of the cholesterol-PEG-ligand conjugate into the niosomes formulation stage was the other option, which was the traditional niosomes formulation approach. [117-119].

**Current status of natural compound loaded nanoparticles used in the treatment of Alzheimer's disease**

From the literature, it is evident that very few molecules are only employed through nanotechnological approaches in the management of Alzheimer's disease (**Table 3**).

**Table 3. Natural compound loaded nano particles for Alzheimer's disease**

| S.No. | Compound | Nanosystem | Carrier |
|---|---|---|---|
| 1. | Curcumin | Nanoparticles | Poly (lactic-co glycolic acid) [120] |
| 2. | Curcumin | Polymerosomes | Maleimide-PEG-Poly(lactide-co-glycolide) [121] |
| 3. | Curcumin | Polymeric Nanoparticles | N-Iso Propyl Acryl Amide (NIPAAM), Vinyl Pyrrolidone (VP), and Acrylic Acid (AA) [122] |
| 4. | Curcumin | Liposomes | Azido-PEG-amine [123] |
| 5. | Curcumin | Solid lipid nanoparticles | 1,2-dipalmitoyl-sn-glycero-3-phosphothioethanol (sodium salt) (DPSH) as nucleophile in the presence of N, N-diisopropylethylamine (DIPEA) [124] |
| 6. | Curcumin | Nano lipid carriers | Carboxylated polyethylene glycol for Cur-loaded Lf-mNLC [125] |
| 7. | Curcumin | Lipid nano capsules | poly(e-caprolactone) [126] |
| 8. | Curcumin | Micelles | Tween-80 [127] |
| 9. | Curcumin and nerve growth factor | Liposomes | Wheat germ agglutinin-conjugated and cardiolipin conjugated liposomes [128] |
| 10 | Curcumin and PQVGHL peptide | Nanoparticles | Poly (lactic-co glycolic acid) [120] |
| 11 | Epigallocatechin gallate | Polymeric nanoparticles | Dopamine-Functionalized Poly Succinimide [129] |

| | | | |
|---|---|---|---|
| 12 | Epigallocatechin gallate | Selenium nanoparticles | Selenium [130] |
| 13 | Ferulic acid | Solid lipid nanoparticles | Compritol 888 ATO [131] |
| 14 | Galantamine | Nanoparticles | Poly (lactic-co glycolic acid) [120] |
| 15 | Galantamine | Chitosan complex nanoparticles | Chitosan [132] |
| 16 | Galantamine | Liposomes | Phospholipids included Di Stearoyl-sn-glycero Phosphatidyl Choline (DSPC), cholesterol (CHOL), and 1,2- distearoyl-sn-glycero-3-phosphatidyl-ethanolamine-methoxypolyethyleneglycol-2000(DSPE) [133] |
| 17 | Galantamine | Solid lipid nanoparticles | PluronicF-127 [134] |
| 18 | Galantamine | Hydroxyapatite nanoparticles | Hydroxyapatite powders, calcium carbonate (CaCO3), ammonium dihydrogen phosphate (NH4·H2PO4), cerium sulphate (Ce (SO4)2) [135] |
| 19 | Grape extract | Solid lipid nanoparticles | Cetyl Palmitate [136] |
| 20 | Huperzine A | Nanoparticles | Poly (lactic-co glycolic acid) [120] |
| 21 | Huperzine A | Microspheres | Poly (D, L-Lactide acid) and Poly (D, L-Lactide-co-glycolide acid) [137] |
| 22 | Huperzine A | Microemulsion (ME) | Capmul® MCM [138] |
| 23 | Huperzine A | Solid lipid nanoparticles (SLNS) | Glyceryl monostearate [139] |
| 24 | Huperzine A | Nanostructured lipid carriers (NLCS) | Capmul® MCM and glyceryl monostearate [140] |
| 25 | Piperine | Nanoparticles | Intranasal Piperine-Loaded Chitosan Nanoparticles [141] |
| 26 | Piperine | Nanoparticles | MeO-PEG-bPCTEMPO [142] |
| 27 | Piperine | Solid lipid nanoparticles | Epikuron 200 [143] |
| 28 | Piperine | Cubosomes | Peceol® and Cremophor RH 40® [144] |
| 29 | Pomegranate seed oil | Nano emulsions | Tween 80 and glyceryl monooleate [145] |
| 30 | Quercetin | Nanoparticles | Poly (lactic-co glycolic acid) [146] |
| 31 | Quercetin | Liposomes | 1,2-Dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1',3'-bis[1,2-dimyristoyl-sn-glycero-3-phospho]-sn-glycerol (cardiolipin [CL]), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-<br>[Carboxy (Poly Ethylene Glycol)-2000] (DSPE-PEG(2000)-CA), and Polycarbonate [147] |
| 32 | Quercetin | Solid lipid nanoparticles | Compritol 888 ATO [148] |
| 33 | Quercetin | Solid lipid nanoparticles | Poloxamer-188 [149] |

| | | | |
|---|---|---|---|
| 34 | Quercetin | Zein nanoparticles | Zein, lysine, 2-Hydroxy Propyl-β-Cyclodextrin (HP-β-CD), Mannitol, Poly Ethylene Glycol 400 (PEG400), Tween 20 [150] |
| 35 | Quercetin | Silica nanoparticles | Polyethylene glycol 3000 monodisperse solution (PEG 3000), Tetra Ethyl Ortho Silicate (TEOS) [151] |
| 36 | Resveratrol | Polymeric micelles | Zein, lysine, 2-Hydroxy Propyl-β-Cyclodextrin (HP-β-CD), Mannitol, Poly Ethylene Glycol 400 (PEG400), Tween 20 [152] |
| 37 | Resveratrol | Solid lipid nanoparticles | CetylPalmitate [153] |
| 38 | Resveratrol | Lipid nano capsules | Poly(ε-caprolactone) [154] |
| 39 | Vitamin E | Polymeric nanoparticles | PEG 1500 Decanyl polymer [155] |
| 40 | Berberine | Polymeric nanoparticles | Hydrogenated Soya Phosphatidyl Choline [156] |

Polyphenols like epigallocatechin (tannin), Quercetin (flavonoid), and Resveratrol (stilbenoid) are showed improved protection against oxidative stress and amyloid plaques formation.

Curcumin (from *Curcuma longa*, Zingiberaceae) is extensively scrutinized under various novel drug delivery strategies using nanotechnology viz, Nanoparticles, Polymerosomes, Polymeric Nanoparticles, Liposomes, Solid lipid nanoparticles, Nano lipid carriers, Lipid nanocapsules, and micelles. These strategies apparently improved the potential outcomes in Alzheimer's disease.

**Conclusion**

Stereotype approaches are spotted to crumple Alzheimer's disease because of their diversified physiological and pathological pathways. A bridge between the research and the patient's reach is demanded to make Alzheimer's therapy. Nanotechnology was convicted to lead some milestones in the new drug delivery systems in neurodegenerative diseases. The basic questions like safety, dosage, routes need to be answered before the development of a nano formulation.

The selection of nanomaterials is the crucial step to making the nano system, which is based on the physical and chemical nature of the bioactive compound. To improve lipophilicity, polymers such as PEG and polysorbates are commonly utilized. Surface area, charge, lipid composition, and drug application strategy all have a significant impact on drug stability, bioavailability, and therapeutic efficacy.

Size is one of the most important parameters that must be strictly regulated; the body will reject nanoparticles larger than 200 nm and cause unpleasant consequences. Similarly, the charge on the surface is important to prevent particle segregation. Moreover, neutral particles are preferred to cross the BBB over anionic and cationic due to toxicity constraints. The best suitable route for delivering the drug is through olfactory mucosa. Much advancements like targeted drug delivery systems such as specific ligands, antibodies, peptides that are having more expression frequency at the BBB will be linked to the nanosystems and can enhance the therapeutic benefits. Undoubtedly, nanotechnology is anticipated to show significant ramifications in the new drug delivery approaches for Alzheimer's disease, and much more research is needed to prosper in the management of the neurodegenerative disease.

**CONSENT FOR PUBLICATION:**

All the authors have approved the manuscript and given consent for publication.

**COMPETING INTERESTS:**

The authors affirm that here be situated not any conflict of comforts concerning the journal of this object.

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