



Review Article

Comparison Study of Various Nano Technology Formulation of Curcumin in Treatment of Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder associated with cognitive deterioration affecting day to day living and behavioural activities. It is commonest cause of senile and pre-senile dementia. In Alzheimer's disease, a peptide referred as amyloid beta aggregates (oligomers), and accumulates in the brain to form deposits called as amyloid plaques. According to the world health organization (WHO), 5% of men and 6% of women of above 60 years are victims with Alzheimer's type dementia globally. In India prevalence of dementia is 33.6%, of which AD contributes approximately 54% and vascular dementia constitutes approximately 39%. Patients with the prolonged use of some Non-steroidal anti-inflammatory (NSAID) drugs such as ibuprofen have lower risk of developing the symptoms of AD; however the chronic use of NSAID can produce a toxic effect on the kidney, liver and GI tract. Recent studies have demonstrated that a curcumin delivery system based on nanoscience and nanotechnology increases the therapeutic potential of this compound. Specifically, several nano-sized carriers such as phospholipid vesicles (liposomes), micelles, solid lipid nanoparticles, polymeric nanoparticles, emulsions, proteins and other molecular complexes have been developed for the efficient delivery of curcumin. Nano particles have demonstrated the enhanced Bioavailability of curcumin including circulation time in the blood. Various nano technology drug delivery system of curcumin showed increased Bio accessibility during treatment of Alzheimer's disease.

Key words: Alzheimer's disease, Dementia, Curcumin, Nano Emulsion, Nano Gel, Nano Suspension, Liposomes.

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INTRODUCTION:

Curcumin, 7bis (4hydroxy3methoxyphenyl)-1,6 heptadiene-3,5-dione is found in the lipophilic extract of the rhizomes of turmeric (*Curcuma longa*). Numerous reports suggest that this natural compound possesses therapeutic benefit such as anti-tumour, anti-inflammatory and anti-oxidant activities. The bioavailability of conventional oral curcumin is low. Therefore the development of an efficient drug delivery system for curcumin is of considerable interest¹.

Alzheimer's disease (AD) is the commonest progressive neurodegenerative disorder of elderly population, characterized by memory dysfunction, spatial and temporal

disorientation and impairment of judgment clinically. The pathogenesis of AD is characterized by loss of neurons and synapses, resulting in gross atrophy across multiple brain regions. The disease is presently hard to reliably diagnose, particularly in its early stages. While an accurate diagnosis can only be obtained post-mortem (via examination of brain tissue in an autopsy), current clinical methods involving brain imaging and neuropsychological testing are only about 85% accurate, that to only at later stages².

Clinical development of drugs for the symptomatic and disease-modifying treatment of AD has generated in both promise and disappointment³. In AD, Biochemical mediators in the inflammation cascade contribute both to neurodegeneration and production as well as accumulation

of the β -amyloid peptide, including interleukin (IL)-1 β , phospho-c-Jun NH2-terminal kinase (pJNK), reactive oxygen species, inducible nitric-oxide synthase (iNOS) and lipid peroxidation products (e.g., 8-iso-PGF2 α)⁴. The neuropathological process in AD consists of neuronal loss and atrophy neurotic plaques are relatively insoluble dense cores of 5-10 nm thick amyloid fibrils with a pallor staining "halo" surrounded by dystrophic neuritis, reactive astrocytes and activated microglia. There is an increased presence of monocytes/macrophages in the cerebral vessel wall and reactive or activated microglia cells in the adjacent parenchyma. The main protein component of amyloid in AD is the 39-42 amino acid (beta) amyloid peptides (A-beta)⁵.

Curcumin has broad-spectrum of therapeutic activities. The low bioavailability of curcumin and poor water solubility

limits its medicinal value⁶. "Nanotechnology-enhanced curcumin: symbiosis of ancient wisdom of the east with modern medical science". In the context of AD pathology, *in-vitro* as well as animal model studies demonstrate that curcumin can have beneficial effects through multiple pathways, such as its strong anti-oxidant activity⁷⁻⁸. Interaction with metal ions and preventing metal-induced aggregation of beta-amyloid⁹⁻¹⁰ and destabilizing preformed beta-amyloid fibrils as well as inhibiting A β aggregate formation¹¹⁻¹³. Thus, administration of curcumin is being seen as a potent therapeutic (and preventive) strategy against AD¹⁴. Nano robot has also been developed for effective cures of disorders which are not amenable to treat. Principles from photodynamic therapy, fullerene chemistry, nano structuring, X-rays, computers, pharmacokinetics and robotics are applied in the design of nanorobot for treatment of Alzheimer's disease¹⁵.

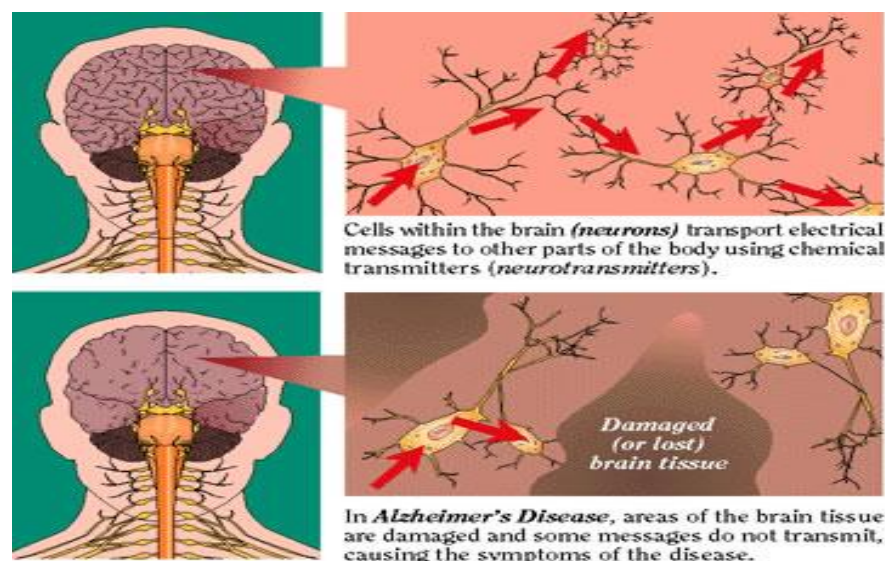


Figure 1: Condition of brain in normal and Alzheimer's patient

Curcumin and Alzheimer's disease:

Globally about 1000 published animal and human studies, both *in-vivo* and *in-vitro* on the effects of curcumin on various diseases have been studied inclusive of epidemiological, basic and clinical research on AD¹⁶.

Mechanism of action of Curcumin on Alzheimer's disease:

AD deteriorates the nerve cells which might involve β ammaton, oxidative damage and mostly observed the formation of beta-amyloid plaques, metal toxicity.

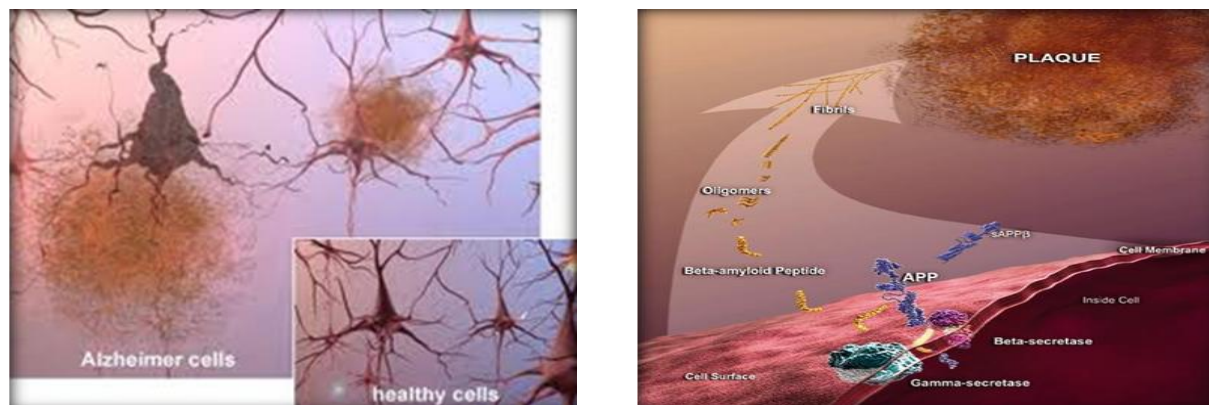


Figure 2: Formation of plaque in brain

Effects of Curcumin on macrophages:

A study carried at UCLA observed that curcumin might help the macrophages to scavenge the amyloid plaques which are observed in Alzheimer's disease. Macrophages play key role in the immune system. They help the body to fight against foreign proteins to effectively eliminate them.

Curcumin was treated with macrophages in blood taken from nine volunteer's six AD patients and three healthy controls. Beta amyloid was then injected. The AD patients, whose macrophages were treated with curcumin, when compared with patients whose macrophages were not treated with curcumin, showed an improved uptake and ingestion of the plaques. Thus, curcumin may support the immune system to clear the amyloid protein¹⁷.

The most marked characteristic feature in AD is the presence of beta-amyloid plaques, which are basically an accumulation of small fibers called beta amyloid fibrils. Because the deposition of beta amyloid protein is a consistent pathological trade mark of brains affected by AD, the inhibition of A-beta generation, prevention of A-beta fibril formation, destabilization of preformed A-beta would be a fascinating therapeutic approach for the treatment of AD. The levels of beta-amyloid in AD mice that were given low doses of curcumin were lowered approximately by 40% compared to those that were not treated with curcumin. Additionally, low doses of curcumin also reduced plaque formation by 43%. Surprisingly low doses of curcumin administered over longer period were more effective than high doses in amelioration of neurodegenerative process of AD. At higher concentration, curcumin binds to amyloid beta and blocks its self-assembly¹⁸. The important chemical features in amyloid beta are the presence of two aromatic end groups and any changes in these groups has profound effect on its activity²⁰. A new biosynthesis of nanoparticles is an interesting method that has attracted significant focus due to their potential use in many applications, such as catalysis, drug delivery biosensor, Anti-microbial and therapeutics. Biological methods of nanoparticles synthesis employing microorganism, enzyme, and plant or plant extract have been proposed as feasible environment friendly alternatives to chemical and physical methods¹⁹. About 40 different nanostructuring operations were reviewed recently. Latest developments in nanomedicine were reviewed.

Development of Nano technology:

Submarine Nano robots are being developed for use in spinal surgery, cancer therapy, etc. Nanoparticles have been developed for use in drug delivery systems and for cure in eye disorders and in early diagnosis. Investigation in nanomedicine is under development of diagnostics for rapid monitoring, targeted cancer therapies, localized drug delivery, and improved cell material interactions, scaffolds for tissue engineering and gene delivery systems.

Nano carrier for Curcumin delivery:

Unsatisfactory pharmacokinetics of oral administration is often observed for poorly water-soluble drug candidates. In

this case, drug delivery systems which permit systemic injection of insoluble drugs are particularly useful. Fortunately, the hydrophobicity of curcumin provides an effective strategy to stably fix curcumin in a hydrophobic domain of various types of nanoparticles. Drug delivery carriers are often classified according to their size (i.e., micro- or nano-) because this is an important factor in characterizing the system²⁰. Nanotechnology-based drug delivery systems for curcumin including liposomes, micelles, Nano gels, Nano Suspension, have been attempted to enhance the oral bioavailability, biological activity or tissue-targeting ability of curcumin²¹.

The Nano Emulsion based delivery of Curcumin:

Nano Emulsion have attracted great attention in research, dosage form design and pharmacotherapy. This is as a result of a number of attributes peculiar to nano suspension such as optical clarity, ease of preparation, thermodynamic stability and increased surface area²².

Nanoemulsions can be prepared by high- and low-energy methods. Both high-energy and low- energy methods can produce stable Nanoemulsions. High-pressure homogenizer or ultra- sound generator can be used for the preparation of nanoemulsion by high-energy emulsification method. Self-emulsification and phase inversion methods-phase inversion temperature and phase inversion composition are low-energy methods for the preparation of nanoemulsions. Low-energy emulsification methods depend on the phase behaviour and properties of the constituents, and they utilize the stored energy of the system to form nano droplets. The emulsification can be brought about by changing the parameters such as temperature and composition, which would affect the hydrophilic lipophilic balance of the system.

Nanoemulsions offer several advantages for the delivery of drugs and are thus receiving increasing attention as drug carriers for improving the delivery of active pharmaceutical ingredient curcumin in treatment of Alzheimer's disease²³. Self-Nano emulsification is only achieved with some oils, surfactants, and co-surfactants at a certain ratio. Selection of an appropriate oily phase is very important, as it influences the selection of other ingredients in oil/water nanoemulsions, generally, surfactant alone cannot lower the oil interfacial tension sufficiently to yield a nanoemulsion; this necessitates the addition co-surfactant to lower the surface tension close to zero²⁴.

The Nano Suspension based delivery of Curcumin:

The curcumin nanosuspension on a lab scale is typically produced by pre-milling (with SDS 0.2%) followed by high pressure homogenization in pure water using a continuous Micron LAB 40 at room temperature, applying 20 homogenization cycles at 1500 bar. Curcumin obtained through nanosuspension over normal/commercial curcumin in being more bio-efficient, suggesting novel delivery strategies for curcumin in therapeutic applications²⁰.the highly stabilized dried nano suspension of curcumin (mean particle size, <80 nm) formulation with remarkable reproducibility and ease of storage. Pharma-cokinetic studies showed that the nanoparticle formulation

significantly improved curcumin bioavailability, with a much greater plasma concentration and six fold higher AUC and MRT in brain. This novel nano suspension curcumin may have great potential for AD therapy²⁵. This study offers significant promises and is worthy of further exploration in attempts to enhance the bioavailability, medicinal value, and application of this interesting molecule from mother nature²⁰.

The Nano Gels based delivery of Curcumin:

Nanogel served as an effective "Nano carrier" for the formulation of lipophilic curcumin by increasing its water solubility, improving its stability, and controlling its release profile²⁶.

The work of Ikeda et al. is an example for the A β anti-assembly strategy. They designed an amphipathic Nano gels that incorporates proteins and controls their folding and aggregation, similar to natural chaperones (proteins assisting the non-covalent folding and/or unfolding). In the case of A β , these Nano gels would inhibit the amyloid genesis process effectively through this mechanism²⁷. But Incorporation of cur-cumin into nanogel did not compromise its cytotoxicity.

The Liposome based delivery of Curcumin:

Liposomes are the most studied nanoparticles for drug delivery. In general, physically stable liposomes are formulated with several kinds of lipid, where the first step is the preparation of the mixed lipids the average diameter of liposomes for typical drug delivery applications is 50-300 nm. It has been confirmed that the lipophilic curcumin is located within the membranes of the liposomes but is absent from the inner aqueous phase the curcumin may be located on the surface of membrane at the hydrophilic/hydrophobic interface, or within the hydrophobic domain. Experimental evidence suggests curcumin is located in the hydrophobic domain of the lipid bilayer membrane¹. Liposomes are of a great importance as nano-carriers due to their relatively large carrying capacity. They have long been used as drug delivery system to the brain, because the particles can entrap the compounds and prevent the rapid elimination or degradation as well as promote the penetration through the BBB which in turn decreases the effective dose among all the applications of

liposomal technology, the development of a suitable liposomal carrier to encapsulate neuroactive compounds is very promising. These liposomes are stable enough to be carried to the brain across the BBB, with the appropriate surface characteristics for an effective targeting and for an active membrane transport. Improvements and adjustments to the liposomal formulation are constantly being explored through the addition of different lipids and targeting molecules. For example, in liposomes lacking cholesterol, high-density lipoprotein can cause disintegration of the liposome, or in liposomes which do contain too much cholesterol, high-density lipoprotein canal so cause leakage of contents. The development of novel therapeutic strategies for neurodegenerative and neurological diseases represents one of the biggest unmet medical needs today²⁸.

CONCLUSION:

1. Nano emulsification is only achieved with some oils, surfactants, and co-surfactants at a certain ratio. Selection of an appropriate oily phase is very important, as it influences the selection of other ingredients in oil/water nanoemulsions, generally, surfactant alone cannot lower the oil interfacial tension sufficiently to yield a nanoemulsion.
2. Nano Suspension offers significant promises and is worthy of further exploration in attempts to enhance the bioavailability, and various medicinal value
3. Nano gels would inhibit the amyloid genesis process effectively through this mechanism. But Incorporation of curcumin into nanogel did not compromise its cytotoxicity.
4. Improvements and adjustments to the liposomal formulation are constantly being explored through the addition of different lipids and targeting molecules. But in liposomes lacking cholesterol, high-density lipoprotein can cause disintegration of the liposome, or in liposomes which do contain too much cholesterol, high-density lipoprotein canal so cause leakage of contents.
5. Based on the above details this novel nano-Suspension delivery of curcumin may have great potential for AD therapy and can be a reference for future studies on formulation of drugs as nano-suspension.

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