# Potential Drug Delivery Pathways for Treatment of Alzheimer's Disease

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**ABSTRACT:** Alzheimer's Disease (AD) has been one of the most prevalent neurodegenerative disorders that majorly affect patients older than 65 years old. The treatment of the disease costs over 1% of the global GDP [1], yet not many new drugs have been developed which can effectively treat AD based on its pathological characteristics. The major challenge in treating brain disorders such as AD is the Blood-Brain Barrier (BBB) which refrains most of the drug molecules from entering the brain. Through reviewing multiple papers from PubMed Central®(PMC), which is an archive of biomedical and life sciences journal literature at the U.S. National Institutes of Health's National Library of Medicine (NIH/NLM), three promising drug delivery pathways have been investigated regarding their capabilities and effectivenesses of transporting drug molecules into the brain, which are inorganic nanoparticles, multifunctional liposomes, and transdermal delivery system. In this paper, brief introductions regarding each delivery pathway were offered, and specific experiment that supported the delivery method was presented. The advantages, as well as drawbacks of each type of delivery pathway, were also discussed in this paper.

## 1. INTRODUCTION

Dementia, also known as a 'major neuro-cognitive disorder', is defined as a group of symptoms that happen because of a disease. AD is a progressive neurodegenerative disease with the typical symptoms of initial memory impairment and decline in cognitive capabilities which essentially impact the patient's normal thinking, memorization, behavior, etc [2]. Alzheimer's Disease (AD) affects more than 50 million people worldwide and costs over 1% of global GDP [1]. Being a prevalent disease that impacts millions of elders worldwide, AD is posting the difficulty of developing a new drug delivery system for a more effective treatment method. The brain being the most complex organ in our body, its circulation is strictly regulated by the structure called the Blood-Brain Barrier (BBB). The Blood-Brain Barrier consists of the microvasculature of the Central Nervous System (CNS) and it tightly controls the CNS homeostasis and protects the brain from any potential toxins, pathogens, inflammations, etc. Endothelial Cells (ECs) are the major player of BBB, and they are held together to form tight junctions which creates a high-resistance paracellular barrier to molecules [3]. Because of the presence of BBB, 98% of small-molecule drugs cannot cross the brain barrier and about 100% of biological drugs cannot cross the barrier. Unfortunately, pharmaceutical companies have not developed effective therapeutics which could penetrate the brain barrier and send the drugs inside the brain [4]. Even though there has not been any clinical therapeutics successfully designed for the treatment of AD, many potential drug delivery pathways for sending drugs across the BBB have been investigated, and each of them serves as a possible therapeutic method for treating brain disorders. It is expected that with those new technologies, the effect of the drug inside the brain should be enhanced. Many previous studies have discussed their findings regarding each drug delivery method, but none of them has analyzed and compared them in terms of their distinctive delivery strategies. In this review, three potential drug delivery methods were introduced and described, and their advantages as well as disadvantages were presented so that people could have a comprehensive picture of the current research status and the characteristics of each method. Two case studies regarding carbon nanotubes and H102 loaded liposomes were included to further demonstrated the possibility of each drug delivery pathway. This review would provide a general introduction to nanodrug delivery, liposome delivery, and transdermal delivery as well as their characteristics to scholars who are interested to learn about potential new treatment methods for AD. This review would help AD patients to understand the mechanisms of drug delivery method behind their medications as well as help the general public to appreciate each small steps that scientists have progressed since those small steps were paramount for the quality of life for all humans in terms of battling with neurodegenerative diseases.

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## 2. DRUG DELIVERY PATHWAY FOR ALZHEIMER'S DISEASE

### 2.1. Inorganic Nanodrug Delivery

#### *2.1.1. Introduction*

Nanoparticles (NP) are colloidal elements incorporated with active drug ingredients and they are a single entity that expresses controlled release in the biological system. NPs are advantageous in the drug delivery system since they improve the kinetic profile and bioavailability of the drug. Moreover, nanotechnology allows for better precision of specific molecular targeting and safe drug delivery to specific sites of action. The sustained release of nanodrug also minimizes the dosage-regimen [5]. There are two types of NPs. Synthetic NPs are prepared from polymeric materials such as poly (ethylenimine) (PEI) and poly (alkyl cyanoacrylates). Inorganic NPs consist of inorganic substances such as gold and silica. Both types of NPs transport drugs through absorbing, entrapping, or covalent bonding, and each of them presents different benefits. NPs are able to pass the BBB's tight junction either by the presence of surfactant in NPs which disrupts the tight junctions of BBB or by BBB impairment because of pathological conditions. NPs can be functionalized with different kinds of ligands or surfactants, and the interaction between ligands and receptors on the ECs triggers plasma membrane invagination, facilitating the release of NPs. This transcytosis process is the most common way of transporting NPs into the brain [6]. In the later section, an experiment investigating carbon nanotubes (CNTs) capable of bypassing the BBB is further discussed.

#### *2.1.2. Carbon Nanotubes Able to Cross PBEC*

In the experiment done by Houmam Kafa et.al., the amino-functionalized multi-walled carbon nanotubes (MWNTs-NH3+) were observed to pass both the in vitro co-culture BBB model made of primary porcine brain endothelial cells (PBEC) as well as in vivo in the mouse brain after intravenous injection and whole-body perfusion with heparinized saline.

During the experiment, Kafa et.al. prepared MWNTs' derivatives, MWNTs-NH3+ and DTPA-MWNTs, then radio-labeled the DTPA-MWNTs with indium. The PBEC were seeded into a 24 well plate and allowed for reaching confluence. The MWNTs- NH3+ dispersions of 5% dextrose solution were added to the cells. After 24h and 72h, light microscopy images were captured. The BBB co-culture Transwell™ system was set up with the tight junctions between adjacent ECs stimulated by a serum-free medium 24h before the uptake studies began. Before the measurement, the trans-endothelia electrical resistance (TEER) was measured and it has to be >200 Ω cm2 for the experiment to start. MWNTs- NH3+ was added to the apical chamber and incubated with the PBEC to test the interactions between MWNTs- NH3+ and the PBEC monolayer through transmission electron microscopy (TEM). A similar process was repeated for the DTPA-MWNTs. The radio-labeled DTPA-MWNTs were used to examine the extent of f-MWNTs transported across PBEC from the apical to the basal chamber.

The study by Kafa et.al. examines the capability of MWNTs-NH3+ to cross the PBEC cells in vitro co-culture BBB model, demonstrating the promising application of MWNTs-NH3+ in transporting drugs to treat brain disease. The passage of MWNTs-NH3+ across the PBEC was examined by ultra-structure imaging, TEM, and scanning TEM. Electron micrographs also confirmed the transcytosis of MWNTs-NH3+. In vivo biodistribution results demonstrated that a sustained amount of f-MWNTs accumulated in mouse brains following systemic administration [7].

#### *2.1.3. Pros and Cons*

CNTs are advantageous nanomaterials because of their special characteristics. Functionalized-CNTs(f-CNTs) can cross plasma membranes and enter the cell through direct translocation or through endocytosis. CNTs also interface with cells and increase the excitability of neurons and it shows intrinsic therapeutic actions in stroke prevention in vivo, which makes CNTs a very promising candidate for treating brain disorders [7]. Overall, Synthetic NPs are advantageous since they provide biological signals to act on specific receptors expressed on ECs, yet they are disadvantageous because there is batch-to-batch variability, the limitation for modification, and poor tracking capacity by imaging platform; Inorganic NPs are easier to control size and shape, tracked by microscopy techniques, and it has simple preparation and functionalization. However, the inorganic NPs are problematic when it does not degrade or they might present undesired toxicity [6].

### 2.2. Multifunctional Liposome

#### *2.2.1. Introduction*

Liposomes are spherical vesicle structures with an internal aqueous compartment surrounded by the hydrophobic lipid bilayer [8]. The Liposomal approach is an extremely popular strategy for encountering brain selectivity through targeting receptors or transporters expressed on BBB. Liposomes can transport both hydrophobic molecules within the lipid bilayer structure, or the hydrophilic molecules inside the aqueous core. Liposomes can be made from various types of lipids, with phospholipids being the most popular type. Conventional liposome formulation is comprised of natural phospholipids and lipids such as sphingomyelin and monosialoganglioside. However, this conventional method of liposomes is proven to be unstable, and the addition of cholesterol to the conventional liposome is needed in order to reduce the rapid release of the encapsulated bioactive compound, thus increasing stability. A modified proposal enhances the transport of liposomes across BBB through the utilization of existing active transport mechanisms, including absorptive carrier

or receptor-mediated transcytosis. Liposomes can be modified and functionalized in a variety of ways for better encapsulation and transportation as therapeutic carriers. The multifunctional liposomal system is a potential treatment pathway for AD as it allows the incorporation of molecules, assisting both BBB transport as well as targeting AD therapy [9]. In the later section, a detailed experiment regarding liposomal delivery was discussed.

#### *2.2.2. Potential H102-loaded Liposome for Treating AD*

In an experiment done by Zheng et.al., the H102-loaded liposomes were proven to be able to penetrate the brain barrier after intranasal administration, thus becoming a promising AD treatment candidate. Previous studies have shown that β-amyloid protein (Aβ) is a critical player in inducing AD. The pathological folding of Aβ and accumulation of Aβ oligomer caused by β-sheets could trigger AD pathogenesis, Therefore, inhibiting β-sheets formation is one of the potential methods to treat AD and H102 peptide is discovered as a β-sheet breaker which can interfere with β-sheet and bind to the Aβ monomer to stabilize its structure, thus inhibiting β-sheets formation.

In the experiment, the H102 liposomes were prepared through a modified thin-film hydration method. The transport capabilities of solution and liposome form of H102 were investigated on the Calu-3 cell monolayer, which was made up of a human airway serous cell line. In the solution group, H102 in solution form reached the platform after 15 mins, which could possibly cause by the ability of chitosan to open tight junctions. The H102 liposome group permeated across the monolayer slowly at first, but the concentration of H102 was higher than the counterpart solution group after 30 min and the concentration increased consistently afterward.

The concentration of H102 in plasma after intravenous (i.v) or intranasal (i.n) H102 treatment as well as brain uptake of the drug was also investigated. The i.n administration of H102 solution showed a fast absorption at 5 min followed by a quick elimination after 45 mins of administration, giving an absolute bioavailability of 11.3%. In contrast, the nasal liposomes administration showed a slower absorption but H102 was still detectable in plasma after 90 mins, which gave an absolute bioavailability of 30.2%, thus demonstrating liposome administration enhanced the nasal absorption of H102 significantly.

The Behavioral experiment, Morris Water Maze Test, was also performed on AD rats with spatial memory impairment induced by bilateral injection of Aβ1–40. A circular tank filled with black-dyed water was divided into 4 equal quadrants, and rats were divided into 7 groups based on their administration conditions. The aim for the rats was to find the invisible platform located in the pool after several training trials. The study result showed that the H102 liposome group was the most capable of successfully locating the platform, followed by i.n H102 solution group. This result confirmed the effectiveness of the intranasal H102 liposome in improving spatial memory impairment induced by AD in rats.

The study shows that the liposomes loaded with H102 could penetrate Calu-3 cell monolayer consistently, thus showing the possibility to deliver H102 into the brain. After intranasal administration of the prepared liposomes and successful delivery into the brain, the hippocampus demonstrated greater absorption of H102 in the liposomes group compared to the solution group. It is also observed that the H102 liposomes could effectively ameliorate the impairment of spatial memory in AD rats.[10].

#### *2.2.3. Pros and Cons*

Liposomes become one of the most popular areas of research since they are highly biocompatible, nontoxic, and they are extremely flexible. The membrane molecules on the liposomes are highly modifiable and the carefully designed liposome can deliver both hydrophilic as well as hydrophobic drug ingredients through the biological membrane. The unique structure of liposomes allows them to carry large quantities of cargo within one compartment. The liposomes are also able to protect their cargo from degradation by plasma enzymes[8]. However, there are certain issues regarding the liposome drug delivery system. Liposomes are not good for oral administration since they will rupture due to the acidic environment of the stomach and lipids will be digested in the small intestine. A large number of liposomes will be taken up by the mononuclear phagocyte system in the bloodstream, leading to a reduction of drugs delivered to the brain, but this issue can be resolved by increasing the volume of drug ingredients for a larger dose. Since the liposome approach targets the transporter system to cross the membrane, there are possibilities that the transporter system will become saturated which hindered further drug delivery. There are also technical issues regarding the stability of liposomes. Liposomes in suspension are likely to fuse together and lead to ineffectiveness, therefore liposomes are often lyophilized or sprayed dried in the presence of trehalose or sucrose to avoid unwanted fusion [9].

### 2.3. Transdermal Delivery

#### *2.3.1. Introduction*

Transdermal Delivery (TD) was developed in the 20th century and it is used by applying drugs to the skin and then transferring the drugs across skin layers. TD is designed to deliver the active drug ingredients across the intact skin and achieved a controlled rate. There are two routes by which drugs can penetrate through the skin, the transepidermal and transappendageal pathways. The transepidermal route starts with crossing through the stratum corneum. The transepidermal pathway can be divided into intracellular and intercellular pathways. The intracellular pathway is responsible for the transportation of hydrophilic or polar compounds that passes through corneocytes. The intercellular pathway transfers the hydrophobic or non-polar compounds. The transappendageal pathway passes molecules through the sweat gland and across the hair follicles [11].

Currently, there are various formulations of TD. Transdermal patches have been the most well-investigated method which could incorporate biochemical enhancers, electroporation, microneedles, thermal ablation, etc, and they can permeate large hydrophilic compounds and proteins. Moreover, nano or microemulsions as semisolid or liquid preparation are also widely used as TDs. Film-forming solutions and sprays are new techniques that are under more examination, but they are also very promising TD techniques that could give patients a better treatment experience [11].

### *2.3.2. Transdermal Patches for Treating AD*

Transdermal patches are characterized as self-contained discrete medicated adhesive patches. The only transdermal patch that is currently under use as a clinical treatment method for AD patients is the rivastigmine patch. The rivastigmine patch is reported as a generally safe, well-tolerated system with excellent adhesion and effective drug penetration. There are three sizes of the patch, 5, 10 15 cm2 with 4.6mg, 9.5mg, and 13.3mg of rivastigmine per day. The drug includes central acting cholinesterase inhibitors as a common pathophysiological characteristic of AD is the cholinergic neuronal loss of the Meynert nucleus in the basal forebrain. This matrix type of transdermal patch is used to treat mild to moderate AD and it only requires one-time application daily. From various studies, it has been approved that a rivastigmine patch is more effective than orally administered rivastigmine since it reaches the greatest therapeutic dose and presents an improved duration of the drug sustainability [12].

### *2.3.3. Pros and Cons*

In general, transdermal patches are well tolerated and easier to use. The drug is delivered directly to the circulation system so it avoids the hepatic first-pass effect and prevents early metabolism caused by the gastrointestinal system, thus achieving great bioavailability. Transdermal patches are also advantageous in terms of a steady and continuous drug delivery, which results in a steady plasma concentration with lower maximum plasma levels. The steady plasma concentration and the continuous drug delivery reduce the tolerability issues and facilitate achieving patients' therapeutic doses, which is extremely pivotal for treating patients who are above 65 years old. The controlled delivery also reduces the toxic effects of drugs.

TD pathway also provides a simplification of the treatment regimen as one patch often covers several doses of drugs. The ease of treatment regimen can effectively reduce the burden of caregivers and induce treatment compliance of older AD patients. TD is easy to use and can be applied independently of meals, which provides flexibility and improve treatment compliance. However, mild irritation of the skin after the application still happens, even though the skin conditions often disappear after the removal of the patches [12].

## 3. CONCLUSION

Alzheimer's Disease has gained attention from the public in recent years, and many pieces of research have been done on the possible drug delivery pathways for treating the neurodegenerative disorder. In the experiment by Houmam Kafa et.al., the carbon nanotubes were proven to be able to traverse the PBEC in the co-culture BBB model, thus becoming a possible candidate as the delivery method. In the experiment by Zheng X. et. al., the H102 loaded liposomes could cross the Calu-3 cell monolayer, thus showing the possibility of crossing the BBB. In the future investigation, more experiments on carbon nanotubes and multifunctional liposomes should be conducted to test the effectiveness of those carriers under various conditions and organisms, and eventually, clinical trials would be conducted to test the effectiveness and safety in humans and to use those new delivery methods in the market. For transdermal delivery, experiments on BBB models or rats can be conducted with various doses of drugs to see if there are possibilities for improvements in kinds and amounts of delivery. More drugs can be investigated so that not only mild to moderate AD patients can be treated with the patches, but also patients who are suffering from severe dementia or patients who only show slight symptoms. For the carbon nanotubes, studies on the effectiveness of real cell barriers should be conducted to further prove the transportation ability. For the liposomes, different drug loads can be tested, which could demonstrate the compatibility of this delivery pathway regarding multiple potential drug molecules. The investigation of new drug delivery pathways would also benefit other brain disorders such as Parkinson's Disease, Amyotrophic Lateral Sclerosis (ALS), epilepsy, etc.

This review is limited in length and only included three potential drug delivery pathways. There must be many other potential pathways that would also be able to pass the BBB and can be used to treat AD, however, this review cannot include all of them. There are only two specific case studies mentioned, which are regarding carbon nanotubes and H102 loaded liposomes, which makes this review narrowly focus more on nanodrug delivery and liposome delivery. To improve, more case studies can be included in order to provide a more comprehensive blueprint about where is the current research status, and where will the focus be in the future.

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