Research Article

ISSN 2639-9466

Nanotechnology & Applications

Recent Trends in Nano-Drug Delivery Systems in the Treatment for Alzheimer 's Disease

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Received: 04 Jan 2025; **Accepted:** 10 Feb 2025; **Published:** 19 Feb 2025

Citation: Sirgio Mejias, Sneed KB, Yashwant Pathak. Recent Trends in Nano-Drug Delivery Systems in the Treatment for Alzheimer's disease. Nano Tech Appl. 2025; 8(1): 1-8.

ABSTRACT

Alzheimer's Disease is a neurodegenerative disease that is an ever-increasing epidemic across the entire world. Alzheimer's Disease is known for the deterioration of the mental abilities of the individual and can also lead to the development of other neurodegenerative diseases. Alzheimer's Disease is a growing epidemic across the world as the population continues to grow and as individuals live longer. The growing neurodegenerative disease epidemic mostly occurs and is more common in older populations. Meaning that potential development of the disease increase with age, but also increased development of the disease if it has already started in an individual. There are many discovered factors that lead to the development of Alzheimer's Disease, all being the accumulation of unwanted molecules in the brain. These molecules are free radicals and amyloid beta peptides. The onset of the disease is characterized by these molecules, among others, and the increasing development of the disease occurs from further accumulation. Limiting the accumulation of these markers would be the key to begin treating those with Alzheimer's Disease.

The difficulty in treating these individuals lies in two main areas, effective drug delivery and effective diagnosing practices. Both of these areas can be addressed through the use of nanotechnology. Nanotechnology or in this application, nanomedicine is the use of nanoscale products to maximize treatment while limiting side effects and adverse effects that are seen in traditional and conventional medicinal practices. Nanoparticles have the ability to be highly customizable through the creation of nanocomposites and nano-polymers, while also being stable, relatively low toxicity, high biocompatibility and availability. The main applications of nanomaterials in the treatment of Alzheimer's Disease is to permeate the blood brain barrier. The blood brain barrier is the highly selective protective layer outside of the brain that serves as the main protector for the brain. The blood brain barrier functions to allow certain nutrients or other needed molecules to enter the brain, while keeping all other molecules out. This barrier makes treating brain diseases difficult since traditional or conventional treatment options to not have the ability to permeate the blood brain barrier without causing further damage to the brain. Nanoparticles and nanomaterials provide a way to permeate the blood brain barrier without causing or introducing the possibility of further harm to the brain, while effectively delivering the needed drugs to treat Alzheimer's Disease directly. Nanomaterials would also be effective is diagnosing Alzheimer's Disease earlier than traditional medicine has been able to. As stated previously, nanomaterials provide a potential way to permeate the blood brain barrier to the brain to detect the amount of any accumulation of the markers for Alzheimer's Disease.

Keywords

Alzheimer's Disease, Nano-Drugs, Neurodegenerative disease.

Introduction

Alzheimer's Disease is a neurodegenerative disease that is characterized by memory loss and declining of cognitive abilities [1]. The cognitive decline that is exhibited in Alzheimer's

Disease is also characteristic of other neurodegenerative disease, Alzheimer's is one of the more studied since the affected population only continues to grow [2]. Knowing this, it is important to look at the effects that Alzheimer's has on the brain in the onset and development of the disease to create a reliable understanding to base treatments on. Alzheimer's Disease has been increasingly studied and is known to be caused by the development of increased amounts of amyloid beta plaques and tau proteins in the body. There is also evidence that suggests accumulation of free radicals in the brain leads to oxidative stress, which results in increased development of Alzheimer's Disease [3]. The accumulation of these peptides, proteins, and free radicals that cause Alzheimer's Disease occur more in older populations, with the risk of developing the disease increasing as an individual ages and only develops at faster rates once the onset of the disease begins [4]. The onset and development of Alzheimer's Disease only further exemplifies the need for more research both the disease and treatment plans based on the fact that the disease continuously worsens with no reliable treatment plan as on now [4].

In response to this information, multiple different Alzheimer's drugs or natural drugs have been developed or discovered to limit or stop the further development of the disease. Among the natural products are those of resveratrol and curcumin. Resveratrol is a naturally occurring compound that acts on the central nervous system [5]. Once the compound is at the proper site, it is known to decrease the amount of amyloid beta plaque buildup and also activate glutathione [5]. Curcumin is another naturally occurring compound which also has the ability to be used in Alzheimer's Disease treatments [6]. Curcumin does not have the exact same reactions or treatments that resveratrol does, but instead mainly has only antioxidant effects [6]. Both of these compounds are naturally occurring making their availability high, but the difficulty in using these compounds in treatments is getting them into the brain where they are needed.

The difficulty in the treatment process is not how to create effective or potentially effective drugs, but in how to administer the drug treatment effectively. The difficulty lies in the inability to penetrate or permeate the blood brain barrier [7]. The blood brain barrier is made up of endothelial cells which are linked in different complex formations making the barrier difficult to deliver drugs across [8]. The difficulty of delivering drugs across the blood brain barrier is due to the main action of the barrier. The barrier acts as a transport relay for the nutrients and waste in the brain and the central nervous system, making the transport highly selective as to what goes into the brain [9]. This highly selective nature of the blood brain barrier is the main obstacle in delivering an effective dose of the Alzheimer's Disease medications that have been developed and cleared for use in recent history [9]. There have been studies into how to bypass the blood brain barrier, most focusing on using the deterioration of the brain, and by side effect the blood brain barrier itself, as an advantage [10]. These studies have also noted that this method does open the brain up to harm beyond the existing disease, making this effort a non-starter [10]. Recent advances in medicine and drug delivery have been highlighted though the use of nanotechnology.

The draw to the use of nanotechnology as part of the treatment for neurodegenerative diseases is the ability to bypass the blood brain barrier. As stated previously, conventional or traditional medicine do not have the ability to deliver an effective dose of a drug across the blood brain barrier, but the specific properties of a nanoparticle drug carrier allow for better delivery of said drug [11]. Nanoparticle drug carrier systems are characterized by their high level of customization in the sense that there are many different nanoparticles that can be used in different formations to accomplish specific tasks [12]. In this sense, nanotechnology has two main advantages in treatment plans for Alzheimer's Disease, the properties that allow for improved drug delivery across the blood brain barrier and the customization to target affected parts of the body. Specifically, the advantageous properties of nanoparticles include specific site targeting, controlled release of drug, stability, biocompatibility, and little to no toxicity in the body [7]. The biocompatibility trait of nanoparticles make them easy to use in combination with not only each other, but also with drugs and natural compounds. This would include the natural compounds discussed previously being resveratrol and curcumin. Nanoparticles or nano-based drug carriers have the ability to deliver these hard to deliver natural compounds to the needed sites, while also being stable and safe for the body [13]. The use of the natural compounds is one example into the benefits that nanoparticles and nano-based drug carriers can provide in the treatment of Alzheimer's Disease. The focus for nanotechnology does not only fall into treating Alzheimer's Disease but can also be used in the diagnosis as well. There are applications for the use of nanoparticles and nanomaterials as diagnosis agents in cancer diagnosis [12]. Nanoparticles and nanomaterials are starting to be used as a means to diagnose Alzheimer's Disease but are able to identify the onset of the disease in an earlier stage than was possible through conventional or traditional methods [1]. With a diagnosis and treatment focused plan, nanotechnology would be able to make massive strides in addressing the Alzheimer's epidemic.

Challenges in Alzheimer's Treatment

The primary challenge in treating neurodegenerative disease like Alzheimer's Disease is bypassing the blood brain barrier. The blood brain barrier is the first line of defense for the brain, being highly selective and only allowing essential nutrients permeate through it [9]. Completed research studies have concluded that there are potentially three routes of drug administration given the selectivity of the blood brain barrier, intranasal administration, systemic administration, and direct administration [9]. These administration routes all have challenges in their own right but do offer some benefits. Intranasal administration does allow the drug to bypass the blood brain barrier but does not deliver an effective does of drug given traditional or conventional drug delivery systems [14]. Systemic administration follows the circulatory system which would allow for the drug to eventually get to the brain, but with lower blood vessel permeability across the blood brain barrier and in the brain, effective drug delivery is a challenge

[14]. Direct administration is administering the drug directly to the brain, which makes the challenge bypassing the blood brain barrier the main challenge to overcome [9]. Permeating the blood brain barrier is a challenge for conventional and traditional drug administration since macromolecules cannot pass the barrier and only needed nutrients are taken in by the barrier, but this means there are pathways that can be used. The main pathways are transport channels that the blood brain barrier uses for nutrients [8]. These pathways can be used through the means of active and passive transport, either going against or with the concentration gradient respectively [8]. Other challenges include degradation by enzymes, which occurs across the entire body, but is focused in areas that need more protection, like the brain and first pass metabolism [14]. These challenges are easier to overcome by avoiding oral administration routes to increase bioavailability since first pass metabolism occurs in the liver, making systemic administration a more difficult venture [9]. To avoid enzymatic degradation, protective drug carrier system could be used to avoid the drug from latching to the enzymes, which would also increase the bioavailability of the drug or treatment [14]. Methods to overcome these challenges are continually studied with nanotechnology emerging as a promising solution. Nanoparticles have the ability to be highly bioavailable and stable, but also small enough to permeate the blood brain barrier through those nutrient channels. The research that has been conducted into the effectiveness of nanoparticles in treating Alzheimer's Disease will be discussed in the following sections.

Lipid-Based Nanoparticles

As with other nanoparticles, lipid-based nanoparticles have the features of stability, biodegradability, and biocompatibility making them suitable starting point for a drug delivery system [15]. Lipid-based nanoparticles are used in many different medicinal applications, mostly being used as drug delivery systems in the treatments for various different diseases [15]. Lipid-based nanoparticles are categorized into three different formulations, being solid lipid nanoparticles, liposomes, and nanostructured lipid carriers. Solid lipid nanoparticles are highly stable and have the ability to bind to many different drugs due to a crystallized structure. While solid lipid nanoparticles are able to bind to many different drugs, they do have a lower loading capacity compared to the other types of lipid-based nanoparticles. Solid lipid nanoparticles have been used in different drug delivery applications when used in nanocomposites or polymeric nano-formulations to overcome this limitation [15]. Using the solid lipid nanoparticles in conjunction with other nanoparticles to increase stability and drug loading capabilities have been researched in their efficacy in treatments for Alzheimer's Disease. Solid lipid nanoparticles have directly been studied in their efficacy of permeating the blood brain barrier. Lipid-based nanoparticles have the ability to use the nutrient channels to permeate the blood brain barrier through both passive and active transport [9]. Solid lipid nanoparticles have also shown the ability to be modified with other nanoparticles to improve their ability to load drugs and properly site target [16]. The increased drug loading capacity allows for more drug to be administered increasing the effective dose in once the target site in reached. The increased ability to properly site target allows for the nanoparticle to deliver the drug or treatment to only affected areas limiting drug or treatment exposure to healthy cells and tissues. This ability to limit drug exposure allows for decreased levels of side effects and adverse effects while also limiting the severity of the side effects as well [16]. Nanostructured lipid carriers are a more developed lipid-based nanoparticle based on solid lipid nanoparticles. These nanostructured lipid carriers address on the low drug loading capacity, ensuring that the nanoparticle itself could load drugs more effectively [15]. Overall, nanostructured lipid carriers are advanced, more modern versions of solid lipid nanostructures, making them suitable in the same applications of solid lipid nanostructures. This increased effectiveness allows for further increases in drug delivery applications and would also benefit from nano-formulations to increase the site targeting ability. The final category of lipid-based nanoparticles are liposomes. Liposomes are organic nanoparticles, meaning they have high bioavailability, in a sphere formulation [17]. Liposomes have two main structures an aqueous center and a phospholipid layer outside of this core. The aqueous layer acts as the drug loading site on the nanoparticle, allowing for a vast variety of different drug loading capabilities, while the phospholipid layer acts as a protective layer to ensure that the drug is delivered to the proper site. Liposomes are able to bind to both lipid-soluble drugs and water-soluble drugs due to the core and phospholipid layer making this nanoparticle able to conduct multi-drug delivery [17]. Liposomes are able to be synthesized with different lipid formations forming the outside layer, allowing for different transport channels to be targeted [18]. This ability allows for researchers to permeate the blood brain barrier theoretically as both *in vivo* and *in vitro* studies have been conducted to test this efficacy [18]. These applications of lipid-based nanoparticles are critical in the treatment efforts for Alzheimer's Disease and have shown promise and the need for further testing in clinical trials as well. The applications of lipid-based nanoparticles discussed have been applied to intranasal administration routes since they would increase the administered dose of the drug [19]. This application allow the nanoparticle an easier pathway to the brain, while bypassing the blood brain barrier [19]. All three forms of lipid-based nanoparticles are used in some formations to allow for increased drug loading and better site targeting making them ideal candidates for intranasal treatment plans since the limitation with this administration route is difficult to administer a proper dose. This is not the only administration route application, as through the use of nano-formulations, lipid-based nanoparticles, especially liposomes, have shown the ability to permeate the blood brain barrier.

Polymeric Nanoparticles

Polymeric nanoparticles are formations of different monomeric nanoparticles to create the most effective drug delivery system for a given administration type [7]. While this is seen as a promising advantage, depending on the composition of the polymeric nanoparticle, changes in the surface composition can cause cytotoxicity. Knowing this, it is important to understand with nanoparticles that combine together to ensure that cytotoxicity does not create a large risk, polymeric nanoparticles are noted to be advantageous in intranasal administration routes [14]. This advantage occurs since polymeric nanoparticles spend less time in the intranasal region because of the emphasis on the size of the nanoparticle [14]. In the formation of polymeric nanoparticle, emphasis is put on understanding not only the drug to properly load, but also the target site to ensure that proper targeting occurs [20]. One of the main factors of nanoparticles that make them suitable to drug delivery systems is the ability to correctly and effective target the affected site and deliver the drug to that site. The importance in this lies with the effort of decreasing the amount and severity of side effects and adverse effects. This is one of the main challenges with traditional medication, since it is the widespread release of a drug that causes side effects and the more drug that is absorbed, the worse the side effect is. This is where the motivation for administering the proper amount of drug treatment to specifically the affected area only to limit the side effects or even eliminate them as a whole. Polymeric nanoparticles are noted to be able to limit side effects since one of the major focuses in the creation of them is to maximize site targeting [20]. Many studies have provided evidence in the efficacy of polymeric nanoparticles. In both *in vivo* and *in vitro* studies, successful site targeting has been noted along with proper drug administration. Polymeric nanoparticles are effective in both site targeting and drug delivery, but another challenge is permeating the blood brain barrier [20]. There are two main focuses for polymeric nanoparticles in this sense, the size of the nanoparticle and the makeup of the nanoparticle. Nanoparticles are small enough that even when combined they are effective is permeating the blood brain barrier through the known pathways [21]. Based on the preclinical studies, both *in vivo* and *in vitro*, polymeric nanoparticles have been shown to effectively target and administer loaded drug doses to affected sites [22]. While the advantages are clear in polymeric nanoparticles, more research should be done to continuously improve upon drug loading limitations, since this will increase the effectiveness of not only the treatment, but only the effectiveness of the polymeric nanoparticle as a drug delivery option. Further studies will allow for better understanding and increased applications in Alzheimer's treatments [22].

Nanocarriers

Nanocarriers simply refer to the application of nanotechnology as a drug delivery system. The efficacy of nanoparticles as effective drug carriers has gained traction in multiple different disease treatments but has only recently begun to be explored to combat Alzheimer's Disease and other neurodegenerative diseases [23]. The main draw for nanocarriers is the potential to effectively permeate the blood brain barrier with causing harm to the brain. Traditional drug delivery system or efforts to effectively deliver anti-Alzheimer's drugs to the brain are known to open the brain up to harm beyond the development of the disease [23]. Nanocarriers are effective in permeating the blood brain barrier since they are adaptable to specific pathways based on which nanoparticles are chosen to carry the drug or used to target a site on the barrier [24]. In the studies that have used nanocarriers to see their effectiveness have found that the ability to effectively target the blood brain barrier and deliver a loaded drug to the site is effective [25]. Nanoparticles and nanocarriers when used in combination with each other create effective drug delivery systems [26]. The effectiveness of the nanocarrier falls on the ability to properly target a site and administer the drug or treatment there. Nanocarriers in there most basic forms are biocompatible, biodegradable, and stable. This is important since the stability of the nanoparticles allow the nanocarrier to effectively bind to the drug and not react in the body which would result in the nanocarrier becoming cytotoxic. The biocompatibility also plays a part in this since the nanocarrier will only target certain sites and not any other part of the body [26]. The importance of the biodegradability of the nanocarriers are to limit exposure to the nanocarriers or nanoparticles after drug administration has finished, making the nanocarrier or nanoparticle easily excretable [24]. Even with these positive effects, there are drawbacks to nanocarriers. In all studies into nanocarriers and nanotechnology as a whole, the ending focus is the need for more research. Nanotechnology is a young science and the use of nanotechnology in medicine is even younger than that, which explains why not many clinical trials have occurred. The advantages the nanocarriers provide are just a starting point for the research efforts and the current limitations of lower than wanted drug loading and potential toxicity will be answered through continued research in this young field of medicine and science.

Additional Potential Nanoparticle Treatments

There are many different types of nanoparticles that have been researched and used in different studies outside of lipid-based nanoparticles and polymeric nanoparticles. Those two types of nanoparticles have been the most researched in Alzheimer's Disease treatments and have provided the most effective results. The following nanoparticles could be discovered to be similarly effective through additional research.

All nanoparticles have the characteristics of being biodegradable [27]. As stated in the previous sections, nanoparticles offer a unique ability to treat a vast variety of different disease all over the body. In most cases, increased biodegradability correlates to increased stability of the nanoparticle. The significance of this is that stable nanoparticles are better at not reacting with other parts of the body causing cytotoxicity in the body. Nanoparticles are a new science so the risks are not fully known, but what is known that limiting any cytotoxicity and side effects or adverse effects will allow for further applications of nanoparticles into clinical trials. The vast number of nanoparticles allows for a vast amount of drug loading possibilities. This would also mean that nanoparticles are able to be modified for a specific administration route like oral or nasal administration. The high customization of a nanoparticle formulation allows for specific treatment models and allows for more stable nano-formulations. The biodegradable nature of nanoparticles allows for safer treatment plans with limited side effects [27]. Since the drug carrier will be broken down in the body faster, it will be less likely to cause adverse effects.

Hydrogels are a form of nanoparticle that has the common characteristics of biocompatibility, stability, and biodegradability, but is also hydrophilic [28]. This hydrophilic nature allows for longer drug administration since they will stay in the body longer than other nanoparticles. When used in combination with chitosan, which is another natural nanoparticle that will be discussed later, efficient drug delivery occurs. The hydrogel was studied through *in vivo* and *in vitro* testing that exemplified that nanoparticle's ability to effectively administer drug doses will circulating through the body. Hydrogels are natural nanoparticles that can be used in combination with other nanoparticles to create stable drug delivery systems and have shown that they can be effective. The hydrogel specifically is table enough to not breakdown and cause cytotoxicity in the body but needs another nanoparticle to ensure an effective drug loading amount. This is a common problem with nanoparticles, but further research could prove beneficial to address this [28].

Carbon nanostructures or nanoparticles are nanoparticles that are categorized by different carbon structures [29]. There are many different types of carbon nanoparticles, including nanotubes, fullerene, and carbon dots to name a few. Carbon nanostructures are more researched in the treatment of other diseases, like cancer, since they are biocompatible. This makes carbon nanostructures more reliable in loading and carrying drugs, making them key in nanoparticle-based drug delivery systems. As stated previously, the research surrounding carbon nanostructures focused on other diseases and not neurodegenerative disease like Alzheimer's Disease. The effectiveness of carbon nanostructures in studies with these diseases have been used to call attention to the possibility of introducing carbon nanostructures to the treatment of neurodegenerative diseases. Carbon nanostructures can be used if they are effective in permeating the blood brain barrier, but this is difficult to do in nanoparticles designed to do this, meaning that more research is needed into this application.

Exosomes

Exosomes are natural nanoparticles that can the extracted from different parts of the body [30]. Exosomes being synthesized from different bodily fluids and structures allows them to be less toxic than other nanoparticles. This source that allows exosomes to be minimally toxic also makes them largely biocompatible and prime candidates for diagnosing diseases. The use of exosomes may not be the exact same as other nanoparticles since they have a natural inclination toward detecting biomarkers, making them prime candidates to detect the biomarkers in the brain during the onset for Alzheimer's Disease. This would be an advantageous application since many times, Alzheimer's Disease is caught too late making the treatment focused on slowing down the disease instead of preventing the disease [30].

Nanobubbles

Nanobubbles are nanosized air pockets that have been noted to have potential as drug delivery systems [31]. Nanobubbles have been known to dissipate shortly after administration, calling into question the efficacy of them as effective drug delivery systems. While the short duration has been found to be a few hours, this does not seem as effective as other nanoparticles as drug delivery systems. Nanobubbles have been used for different screening procedures, which means they could be used in a similar way in Alzheimer's screening and diagnosis.

Nano-emulsions

Nano-emulsions are a liquid nanoparticle that is relatively stable through surface properties [32]. Nano-emulsions can be used in areas that can easily bypass the blood brain barrier, since there is not effective way of nano-emulsions permeating it. This administration route would be intranasally, but this causes questions about how much loaded drug is administered to the brain. This is a similar problem with oral administration, but this would also include first pass metabolism in the liver, further decreasing the effective dose delivered to the brain if it is delivered at all. Overall, the intranasal route would be more effective, but as with many other nanoparticles, more research is needed to discover if the nanoparticle if effective at delivering the drug to the brain.

Chitosan Nanoparticles

Chitosan-based nanoparticles are a natural nanoparticle that can be extracted and synthesized from chitin from sea life [14]. One of the main factors that makes chitosan-based nanoparticles effective is the ability to have a controlled release of the drug [33]. Chitosan-based nanoparticles are highly customizable, making them promising is both drug loading and drug delivering applications. In many cases, chitosan is used a protective layer that allows for a controlled drug release inside the body [16]. It has been noted that chitosan has high mucoadhesion properties, making it valuable for any intranasal drug administration routes. In these applications, chitosan could play a pivotal role in in Alzheimer's treatment. The mucoadhesive properties would allow for increased concentration of drug loaded nanoparticles in intranasal administration, which could increase the effective dose administered. The protective and controlled release properties would protect the nanoparticle to allow for drug release over a longer period of time allowing for more drug to be absorbed in the affected areas.

Polyphenols

Polyphenols can combine with many different nanoparticles to aid in drug delivery [34]. Many studies have used polyphenol-based nanoparticles to administer curcumin and resveratrol, which are both natural compounds that can be used in Alzheimer's Disease treatments. On of the main drawbacks for polyphenol is an overall instability that lends itself to increased cytotoxicity. More research is needed to find the true purpose for polyphenol and the nanoparticles it is part of, but being used as a drug carrier for Alzheimer's drugs could be a suitable application for it if used in combinations with other more stabilizing nanoparticles like chitosan.

Treatment Routes

Throughout the description of the different types of nanoparticles that have been researched for their efficacy in Alzheimer's treatments there have been mention of many different treatment routes. One of the more popular administration routes for treatment was intranasal administration. Intranasal administration is the drug treatment through the nose to the brain [35]. It was noted that intranasal administration is more effective than oral or systemic administration since the bioavailability of the drug is more in intranasal compared to the others. Traditional drug administration has not been effective since a small portion of the drug actually is delivered to the brain. Through the use of nanoparticles as drug delivery systems, they can deliver the drugs through the nasal passage to the brain, allowing for increased bioavailability of the drug in the brain [37]. This increased bioavailability of the drug allows for more of the drug to be absorbed by the affected areas, allowing for increased treatment.

Nanoparticles can be used to target different areas in the brain to increase bioavailability at different biomarkers [37]. As stated previously, the accumulation of amyloid beta peptides, tau proteins, and free radicals are all associated with the onset and continued development of Alzheimer's Disease. Targeting these biomarkers allows for increased bioavailability in the brain regions that need the drug. Targeting the tau protein would not only be beneficial in the diagnosis of Alzheimer's disease, but it would also be beneficial to deliver anti-Alzheimer's drugs to that site as well [38]. This could also be attributed to targeting amyloid beta peptides in the brain. Instead of targeting free radicals directly, the mitochondria is targeting since the free radicals are formed in this area of the cell [39]. The mitochondria can often be put under oxidative stress which directly leads to the release of free radicals in the brain, so by targeting the mitochondria, free radicals can also be treated as well [39]. This is also an application for antioxidants since those can easily be attached to the mitochondria which will further limit the number of free radicals that are released into the brain. Nanoparticles can also be combined with different enzymes like acetylcholinesterase to reduce oxidative stress [40]. Acetylcholinesterase has the natural effect of reducing oxidative stress which would be beneficial in antioxidant treatments. Nanoparticles can also be used to target specific neurons that are affected by Alzheimer's Disease [41]. The targeting of specific neurons would allow for nanoparticles to address the most problematic areas of the brain to have treatment and drug focused on the most affected area.

In traditional medicine, the central nervous system is difficult to treat, making neurodegenerative diseases increasingly more difficult to treat [42]. The main efforts of using nanoparticles in Alzheimer's Disease treatment is to bypass the blood brain barrier [43]. Nanoparticles are also increasingly helpful in detecting biomarkers to discover neurodegenerative disease in their earlier stages, where they can be prevented [43]. Nanoparticles have also been studied to address signaling pathways that have been damaged form the development of Alzheimer's Disease [44]. There has also been research into multi-drug applications of nanoparticles to allow for increased drug administration [45]. These applications show that efforts to find effective applications of nanoparticles are continuing since the nanoparticle show promise in the drug delivering ability. It is also important to note that the nanoparticles themselves are known to bypass the immune system response that normal drug cause [46]. This makes nanoparticles and nanotechnology significant in the treatment of all diseases since the normal side effects can be limited or eliminated due to site specific drug release. Other nanoparticle applications involved external stimuli to create a specific response. Through the use of electrospinning the nanoparticles, it allows the nanoparticles to have faster drug releases [47]. Another external application is the use of ultrasound to create a short pause in the selectivity of the blood brain barrier, allowing for drug administration to occur easier [48]. This application is potentially dangerous as this could also allow damage to the brain to occur. But if used in conjunction with other therapeutic effects like the electro-spun nanoparticles, then quick drug administration could occur without worrying about bypassing the blood brain barrier.

Conclusion

The use of nanoparticles in the treatment of Alzheimer's Disease and other neurodegenerative disease is a relatively new application, but one that produces many promising outcomes. From the use of using nanoparticles in diagnosing Alzheimer's Disease to using nanoparticles to target specific sites in the brain to administer drugs. The previous sections all show the vast applications of nanoparticles in Alzheimer's treatment. There are many areas in which nanoparticles need to improve, like effective drug loading and decreased toxicity or increased stability. The main nanoparticles that have been researched in these applications are polymeric nanoparticles and lipid-based nanoparticles. Both of these nanoparticles have the application for specific site targeting and drug administration. While these are the most promising nanoparticles to use, the most effective administration route is the intranasal route. This route allows for the blood brain barrier to be bypassed and the drug delivery systems to go directly to the brain. These administration sites and nanoparticles are not the only ones that are effective, but they are the ones that have the most research conducted for them in both *in vivo* and *in vitro* studies. Further applications for nanoparticles in neurodegenerative disease treatments would be to expand on the benefits of the nanoparticles like their bioavailability, biodegradation, and stability. These characteristics are the leading reasons for the consideration for nanoparticles as part of different therapeutic and drug administration responses. Nanotechnology is a blossoming new science that can lead to massive improvements in how drug are administered for some of the most detrimental diseases that plague the world today. The main focus for nanotechnology in medicine and Alzheimer's treatment is to make them as efficient and safe as possible through additional research and eventual clinical studies.

Future Trends

Many of the benefits that nanoparticles and nanotechnology as a whole can help further understand Alzheimer's Disease to create proper treatment plans, also come with their own difficulties. Most nanoparticles are relatively stable and safe for use, but some of the most beneficial nanoparticles or most useful nanoparticles have higher cytotoxicities [49]. In many research trials, the use of multi-functional nanoparticle formulations have been thought of as an answer to many problems seen in nanotechnology applications for Alzheimer's treatment [24]. The term multi-functional could also reference multi-targeting nanoparticles, which have also been noted to need further research to find if the proposed efficacy is accurate [49]. This application of nanoparticles is intriguing since it would allow for better targeting and aggressive treatment plans for Alzheimer's Disease. The reason for additional research be done into this application is while there are proposed benefits, there are potential drawbacks, like cytotoxicity and effective drug delivery to the brain [24]. Among these clear references to potential risks that could occur due to the use of nanoparticles, there is also clear support for the continuation of research into these applications. The benefits and potential risks that the application of nanoparticles in Alzheimer's treatments are why additional research and more clinical trials are needed. Additional research is needed to further make improvements in specific applications before they are applied in clinical trials and also throughout clinical trials. Continued studying and educating about the development and severity of not only Alzheimer's Disease, but other neurodegenerative diseases will also aid in future applications of nanomedicine as a field of study. Clinical trials are needed to observe the benefits and potential risks in real applications. As stated previously, the number of people affected with Alzheimer's Disease only grows exponentially every decade making this need for continued development and action important for the future of nanomedicine and neurodegenerative diseases.

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