CHAPTER

23

Pharmacokinetics and pharmacodynamics of various novel formulations targeting Alzheimer's disease

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1. Introduction

Alzheimer's disease (AD), a condition that causes the degeneration of intellect cells, is primarily responsible for dementia, which is defined as a loss of mental capacity and self-reliance in daily tasks. It was proposed that the two main causes of AD, which is considered to be a complicated disease, are cholinergic and amyloid [1]. Aging, hereditary feature, head slash, vascular illnesses, contamination, and environmental element are other risk factors that have an impact on the condition. Only two model of drugs now bless to treat AD are cholinesterase enzyme inhibitors and N-methyl D-aspartate (NMDA) antagonists, both of which narrowly serve to cure the symptoms of AD rather than preventing or curing it [2]. In order to grow effective therapies that can slow or alter the progression of AD, research is currently concentrating on understanding the pathology of AD by focusing on a number of mechanisms, including deviant tau protein metabolism, -amyloid, inflammatory response, and cholinergic and free radical damage. The drugs that are now available on the market as well as possible options for novel AD therapies, including as disease-modifying therapeutics (DMTs), chaperones, and natural compounds [3], will be covered in this chapter. The pharmacokinetic and pharmacodynamic characteristics of various AChEIs vary [4]. For instance, although rivastigmine is predominantly eliminated by liver and intestine metabolism, donepezil and galantamine are primarily eliminated through hepatic metabolism. Rivastigmine is a "pseudoirreversible" inhibitor of butyrylcholinesterase and acetylcholinesterase, and its elimination half-life after oral administration is just 1–2 h [5]. While galantamine and donepezil just and temporarily block acetylcholinesterase. The elimination half-life of galantamine is 6–8 h while that of donepezil is 70 h [6]. The PK/PD characteristics of the drug substance affect the efficacy for the cure of AD since the duration of effort is prolonged for the time due to the suppression of acetylcholinesterase and butyrylcholinesterase for about 8.5 and 3.5 h, respectively. Also, it will cover a brief description of Alzheimer's disease, different therapy formulations and technologies, and a brief overview of pharmacokinetic and pharmacodynamic research [7,8].

2. Alzheimer's disease

The neurological illness in AD, which primarily affects elderly individuals, is progressive, diverse, complex, and incurable. The widely recommended treatment includes cholinesterase inhibitors and NMDA-receptor antagonists;

Alzheimer's Disease and Advanced Drug Delivery Strategies
https://doi.org/10.1016/B978-0-443-13205-6.00027-3

their combo therapy, however, only offers momentary symptom relief. Worldwide, researchers have made genuine efforts to identify novel targets, identify novel therapeutic compounds, and develop novel AD therapies. This brief book chapter seeks to **summarize** current advances in drug development and innovative AD therapies that work on a number of targets.

2.1 Pathogenesis and clinical features in AD

There is a wide area of study being done to fathom the pathophysiology of AD and create potent treatments. AD is a neurodegenerative condition that progresses and is quite complex. It is one of the main contributors to dementia cases worldwide. About 5.3 million human being in the US alone have AD, of which 5.1 million are 65 or older and 200,000 have the disease at a younger age [9]. Li N.M et al. According to reports, the histopathological features of AD include intracellular aggregations of neurofibrillary tangles (NFTs), which are construct of hyperphosphorylated microtubule-associated, and extracellular aggregates of plaques. In the locus coeruleus, transentorhinal, and entorhinal regions of the brain, there is a concentration of A that causes tangle formation [10]. They explained the cause, pathophysiology, and elements involved in the course of AD because A and NFTs are thought to be the main players in the illness [10–12].

Amyloid pathogenesis Amyloid precursor protein (APP), an essential protein on the plasma membrane, is first already digested by -secretases (BACE1) and -secretases to generate insoluble A fibrils. Following this, An oligomerizes, diffuses into synaptic clefts, and disrupts synaptic signaling. It then polymerizes into immobile amyloid fibrils that clump together to form plaques. This polymerization causes kinases to be activated, which in turn causes the microtubule-associated protein to be hyperphosphorylated and polymerized into insoluble NFTs. This adds to neurotoxicity by encouraging microglial activation and a local inflammatory response [12–14].

3. Currently available drug molecules for the management for AD

It is beneficial to have a general understanding of the current treatments before delving into the detailed specifics of novel therapy options for AD management. In order to address ways AD affects a person's memory and cognitive performance, numerous pharmacological medication designs have been in development for a long time. Initially, these treatments were prescribed in line with the cholinergic and glutamatergic theories [15]. Another hypothesis connects the evolution of AD to the loss of pre- and postsynaptic neurons' Nicotinic acetylcholine receptors (nAChRs) of subtype a7 or a4b2 and muscarinic acetylcholine receptors (mAChRs) of subtype M2. From the authorized ChEIs as standard medication therapy to strengthen the cholinergic system are galantamine, rivastigmine, and donepezil [16]. In order to maintain ACh levels and control neurotransmission, this ensures that ACh will bind to nAChRs and mAChRs. Memantine, on the other hand, To stop intracellular calcium (Ca2+) entry and the ensuing excitotoxicity that results in neuronal degeneration in AD, an agent specifically targets the NMDA glutamate receptor. The results of the global evaluation instruments show that the cognitive function of AD patients who take ChEIs and memantine is enhanced [17,18].

3.1 Galantamine

A competitive and reversible inhibitor called galantamine may bind to the nAChRs' allosteric site. The therapeutic significance of galantamine against mild-to-moderate AD has been determined by numerous systemic evaluations. Galantamine doses of 24 and 32 mg administered daily to AD patients showed improved cognitive performance [19]. Wilkinson DG et al. performed similar study in the United States has verified similar data. After taking 24 mg of galantamine per day, patients' cognitive abilities were evaluated, and the findings were encouraging and reliable over a period of 6- to 12-months. Patients who received the same flexible galantamine dose escalation (24–32 mg/day) over a period of 4 weeks likewise reveal greater proficiency in controlling fundamental per diem venture on both a fundamental and instrumental level [20]. Galantamine has linear pharmacokinetics and is around 90% bioavailable. It has a limited protein binding capacity and a considerable volume of dispersion. Galantamine increases cholinergic tone by inhibiting both muscle and brain acetylcholinesterase through central and peripheral actions [21–23].

3.2 Rivastigmine

Rivastigmine functions as a steady -adaptable carbamate avoidance targeting the pair acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), which are predominantly present in the cerebrospinal fluid of

individuals with Alzheimer's disease (AD) [24]. Rivastigmine has 1.8−2.7 L/kg volume of distribution, 40% protein binding and 1.5 h half-life. And renal cl = 2.1−2.8 L/h, it is rapidly metabolized by hydrolysis induced by cholinesterase [25]. To produce the decarboxylation metabolite NAP226-90, rivastigmine undergoes substantial metabolism, principally through cholinesterase-mediated hydrolysis. The primary method of elimination for the metabolites is renal excretion [26]. The amount of medication that is eliminated in feces is quite small—less than 1%. Rivastigmine is a reverse cholinesterase inhibitor and parasympathomimetic.

3.3 Donepezil

The drug donepezil also called donepezil hydrochloride is an uncompetitive, reversible AChE inhibitor that has long been validate for symbolic therapy for mild to moderate AD in 1996 [27]. Donepezil is administered orally and is slowly absorbed through the digestive system. Within 15−21 days after dosing, steady-state concentrations are extend with a Tmax of 3−4 h and 100% bioavailability [28]. According to the Canadian monograph, the Cmax of donepezil tablets at a dosage of 5 mg is thought to be 8.34 ng/mL. The AUC for tablets containing 5 mg of the drug has been calculated to be 221.90−225.36 ng. The extravascular compartments are where it is primarily disseminated. Donepezil, whose concentration in the cerebrospinal fluid at the aforementioned doses was 15.7%. Eight According to the FDA label for donepezil, the vd at steady-state ranges from 12 to 16 L/kg 96% of the drug donepezil is associated with proteins, with 75% of it with albumin and 21% with alpha-1-glycoprotein [29]. It is metabolized in the liver via first-pass metabolism, mainly by CYP3A4 and CYP2D6. Donepezil has a 70 h elimination half-life on average. This drug's apparent plasma clearance ranges from 0.13 to 0.19 L/h/kg on average [30,31].

3.4 Memantine

An NMDA receptor antagonist called memantine is exert to cure Alzheimer's patients who have mild to moderate dementia. This drug prevents the persistent activation of glutamate-activated NMDA receptors that ordinarily results in calcium influx into cells [32]. Increased cognitive and other positive central nervous system benefits show that this improves the signs of Alzheimer's dementia [33]. Meantime's normal vd is 9−11 L/kg with protein fetter is 45% [34,35]. Memantine gained FDA marketing approval in 2003 to primarily intent moderate-to-acute AD in comparison to other ChEIs. Memantine is a type of uncompetitive NMDA receptor antagonist that causes adverse effects by preferentially preventing the activation of NMDA ion channels [35]. This effect can be produced by carefully adjusting the dosage intake. The release of apoptosis-inducing substances may be blocked by lowering the NMDA ion channels' permeability to Ca^{2+}, which may mediate regular neuronal activity. Surprisingly, memantine clinical studies to treat moderate to severe AD fell short of expectations because the tested medicine just postponed the onset of cognitive decline. Additionally, there are findings that suggest combining memantine with other ChEIs in a treatment plan to perhaps delay or stop the development of AD. Memantine has been linked to an improved cognitive deficit in AD, according to reports. Overall, memantine treatment suggested a positive future for those with moderate-to-severe AD, but additional studies with wide scope are encouraged to demonstrate the use of this drug's efficiency and safety [35].

4. Treatments for AD in the CNS: Clinical pharmacokinetics and pharmacodynamics

The clinical pharmacology of the Alzheimer's medications that are currently approved reveals various possible reasons why clinical trials have failed. Interpedine and verubecestat were the most recent Alzheimer's disease drugs to fail in the fall of 2017 [36]. Because Alzheimer's is a degenerative illness, changing medication concentrations in the brain could result from developing brain pathology. Other factors include CSF concentrations after dosing. It is thought that this is the reason for the decreased drug efflux from CSF because the drug is a P-gp substrate and P-gp protein is destroyed as Alzheimer's disease advances [37]. One could anticipate that donepezil would accumulate [38]. In another study a single autopsy patient's brain tissue concentration of the NMDA receptor antagonist memantine [39]. However, such data may be too scant to interpret. Although acetylcholinesterase (AChE) inhibitor rivastigmine [25]. There is little information on the effectiveness of PD measures in Alzheimer's patients. For instance, a previous review observed issues with employing AChE activity measures as an end measure due to confounding by several factors like food, concurrent medication, or time of lumbar puncture, which made the effect size of PK/PD studies more challenging to interpret. Furthermore, even though some studies use plasma concentrations to link

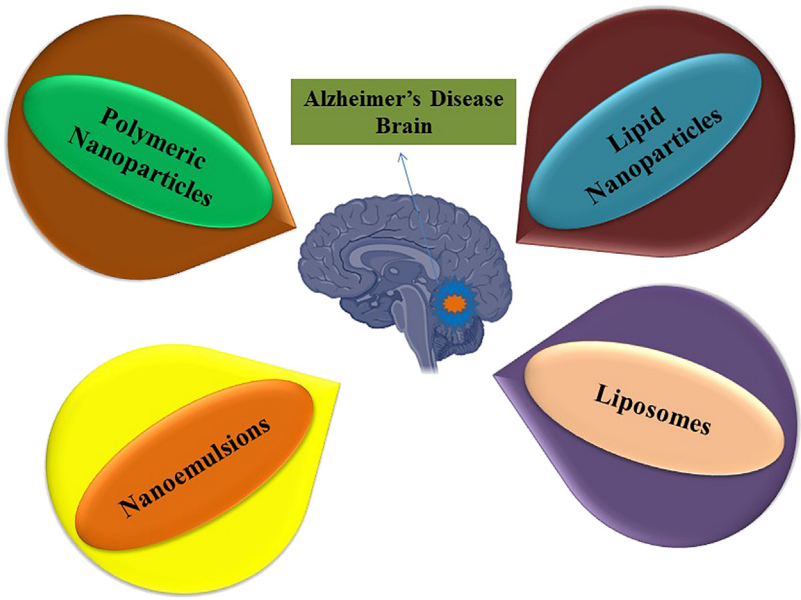

FIG. 23.1 Nanoparticle delivery system for the management of AD.

treatment results, plasma concentrations need to be confirmed as a reliable substitute for the target site first. The advancement of new therapeutic approaches for conditions of the central nervous system (CNS) in animals to humans remains difficult, with a high attrition rate in the development of CNS medications, despite their important contribution to the burden of world disease. Pharmacokinetics/pharmacodynamics (PK/PD)-related issues, such as ineffectiveness or poor initial dosage management, can help to explain why clinical trials for CNS treatments fail. CNS-acting medicines must undergo a focused evaluation in first-in-human trials to see how their PK/PD differs from that of animal models and to determine the best dose [40] (Fig. 23.1).

5. Nanoparticle delivery system for the management of AD and their PK PD

5.1 Liposomes

The spell "Lipos" (fat) and "Soma," (body), are the birth of the "liposome." The term of a liposome refers to its structural constituents, the phospholipids, rather than to its size, and it can be created in a variety of sizes using either unilamellar or multilamellar construction [41].

The pharmacokinetics (PKs) of liposomes as nanoformulations for Alzheimer's disease involves understanding how liposomes interact with biological systems. These properties can affect their stability, circulation time, and ability to cross biological barriers [41].

Studies have shown that liposomes can influence their facility to tetchy the BBB. Surface charge can also influence the interaction of liposomes with the BBB. Positively charged liposomes have been shown to have better brain penetration compared to negatively charged liposomes due to their interaction with the negatively charged BBB [41,42].

The PK of liposomes can also be influenced by the route of administration. Intravenous administration is commonly used for liposome-based nanoformulations. However, further passage of application, such as intranasal and intraperitoneal administration; have also been investigated for liposome-based nanoformulations for Alzheimer's disease. The PK of liposomes as nanoformulations for Alzheimer's disease involves understanding how their physicochemical properties influence their stability, circulation time, and ability to gainsay the BBB and accumulate in the brain. The PK of liposomes is influenced by their size, surface charge, and lipid composition, as well as the route of administration. Further research is needed to optimize the PK of liposome-based nanoformulations for Alzheimer's disease and to better understand their potential therapeutic benefits and risks [43–45].

The pharmacodynamics (PDs) of liposomes as nanoformulations targeting Alzheimer's disease involves understanding how the liposomes interact with biological systems and how they affect the underlying pathology of AD. Liposomes can be designed to target specific biomolecules or pathways involved in AD, such as amyloid-beta (Aβ) plaques or tau protein. For example, liposomes can be decorated with ligands that recognize and bind to Aβ or tau protein, which can enhance their specificity and affinity for these targets. Once liposomes bind to their target, they can initiate various PD effects. One potential PD effect is the reduction of Aβ aggregation and accumulation. Liposomes can be designed to encapsulate drugs or small molecules that can retard Aβ aggregation or hype Aβ clearance. For example, one study found that liposomal curcumin reduced Aβ accumulation in the brains of transgenic mice with Alzheimer's disease. Another potential PD effect of liposomes is the reduction of neuroinflammation. Liposomes can be designed to encapsulate antiinflammatory drugs or small molecules that can inhibit the activation of immune cells or the production of proinflammatory cytokines. For example, liposomal ibuprofen has been shown to reduce neuroinflammation and improve cognitive function in a mouse model of AD. Liposomes can also be used to deliver genetic material, such as small interfering RNA (siRNA), to target specific genes or pathways involved in AD. For example, one study used liposomal siRNA to target BACE1, an enzyme involved in the production of Aβ. The liposomal siRNA was able to decline Aβ levels in the brains of transgenic mice with AD and improve their cognitive function. In summary, the PD of liposomes as nanoformulations targeting AD involves their ability to interact with specific biomolecules or pathways involved in the disease and initiate therapeutic effects, such as reducing Aβ accumulation or neuroinflammation. Liposomes can also be used to deliver genetic material to target specific genes or pathways involved in AD. Further research is required to optimize the PD of liposomes for AD and to better understand their potential therapeutic benefits and risks [46–50].

5.2 Dendrimers

Dendrimers are a further interesting nano formulation. Branching nanoscale polymers called dendrimers have the ability to encapsulate hydrophilic medicines. Dendrimers have been utilized to target particular cell types, and improve drug solubility.

Dendrimers are spherical, highly branching polymers that can enclose medications to enhance delivery to target cells. Dendrimers' PK characteristics may vary depending on their size, surface chemistries, and functional groups. Dendrimers can be designed to target particular types of brain cells and, increasing medication concentrations in the brain and minimizing side effects [51,52].

Drug encapsulation efficiency: Dendrimers can encapsulate drugs within their interior or on their surface, which can defend the drug from deterioration and improve its bioavailability. The drug encapsulation efficiency can vary depending on the drug and dendrimer properties.

Drug release rate: The rate at which dendrimers release their encapsulated drug can affect the PK of the drug. Dendrimers can be designed to release their drug payload quickly or slowly, depending on the desired effect.

Circulation time: Dendrimers can prolong drug circulation time in the bloodstream, which can increase drug exposure and reduce the frequency of dosing. The circulation time of dendrimers can vary depending on their size and surface chemistry.

Clearance: Dendrimers can be rid from the bloodstream by the reticuloendothelial system, which can affect their PK. Dendrimers can be designed to have longer circulation times by reducing their clearance.

Dendrimers are attractive nanoformulations for targeting AD overall because of their distinctive PK characteristics. They can raise drug concentrations in the brain, enhance drug solubility and permeability, and lessen side effects. To completely comprehend their PK in clinical settings and improve their design for particular medicines and applications, more study is necessary [53–55].

By boosting drug absorption by target cells and lowering drug degradation and elimination, dendrimers can improve treatment efficacy. Dendrimers can increase drug selectivity by focusing on particular brain cell types, including neurons or glial cells. By encasing antiinflammatory or antioxidant substances inside their structure, dendrimers might lessen oxidative stress and inflammation in the brain. Dendrimers interact with A-peptides and facilitate their elimination in order to lessen amyloid-beta (A) aggregation and toxicity [56]. Polyamidoamine (PAMAM) dendrimers conjugated with galantamine, a cholinesterase inhibitor, have been shown to enhance drug uptake by neurons [57]. Folate receptors on neurons, have been shown to build-up the confinement of antiinflammatory drugs, such as methotrexate, to brain tissue. The dendrimers were able to reduce inflammation and oxidative stress in mouse models of Alzheimer's disease [57]. Polyethylene glycol (PEG)-modified dendrimers encapsulating Aβ-targeting peptides, such as KLVFF, have been shown to reduce Aβ aggregation and toxicity in vitro and in vivo. The

dendrimers were able to bind to Aβ peptides and promote their clearance by microglial cells [58]. Dendrimers, in general, exhibit special PD features that make them potential nanoformulations for the therapy of Alzheimer's disease. They can improve drug absorption and selectivity, lessen oxidative stress and inflammation, and lessen An aggregation and toxicity. To completely comprehend their efficacy and safety in clinical settings and to improve their design for particular medications and applications, more study is necessary [58,59].

5.3 Solid lipid nanoparticles (SLNs)

SLN devices have a lipid-forming core at physiological and ambient temperatures. The pharmacokinetics of SLNs depends on various factors. SLNs can be administered via copious passage such as oral, intravenous, intranasal, and transdermal routes. However, the most effective route for SLNs to target AD is the intravenous route due to the call for the particles to pass over the BBB and reach the brain [60]. SLNs have been shown to have an enhanced the circulation time in the bloodstream, allowing for sustained drug release. This sustained release is beneficial for the treatment of Alzheimer's disease, which is a chronic and progressive disease. The sustained release of drugs from SLNs can provide continuous treatment and reduce the frequency of dosing [61]. Donepezil-loaded SLNs can improve the solubility and bioavailability of donepezil and enhance its delivery to the brain [62]. Another example is the use of SLNs to deliver curcumin, a natural compound with antiinflammatory and antioxidant properties. However, the poor bioavailability and solubility of curcumin limit its therapeutic efficacy [63]. In both of these examples, the pharmacokinetics of SLNs involve the sustained release of drugs, improved bioavailability, and enhanced delivery to the brain. These characteristics make SLNs an attractive drug delivery system for the treatment of Alzheimer's disease. However, further research is needed to optimize their formulation and ensure their safety and efficacy [64].

The pharmacodynamics (PDs) of solid lipid nanoparticles (SLNs) in the cure of AD involves the interaction of the SLNs with the biological targets that grant to the blooming and progression of the disease [61,64]. SLNs can be used to target specific biological pathways involved in AD, such as the accumulation of amyloid beta plaques and neurofibrillary tangles, inflammation, and oxidative stress. The SLNs can be loaded with drugs or other therapeutic agents that can act on these pathways, either by inhibiting their formation or by promoting their clearance. One example of an SLN-based therapy for AD is the use of SLNs to deliver curcumin, a natural compound with anti-inflammatory and antioxidant properties, to the brain. Curcumin has been shown to reduce amyloid beta accumulation and better cognitive function in animal models of AD. However, curcumin has poor solubility and bioavailability, which limits its effectiveness as a therapeutic agent. These factors can affect the stability and bioavailability of the SLNs, as well as their skill to rood the blood-brain barrier and target specific biological pathways. Essentially, using SLNs to carry therapeutic drugs to the brain and reach particular biochemical pathways in the cure of AD offers a promising method. To improve their formulation and guarantee their security and effectiveness, additional study is required [65,66].

5.4 Polymeric NPs (PNPs)

PNPs serves drug delivery vehicle to target AD. The PK of PNPs depends on various factors such as the polymer arrangement, size, surface charge, and route of administration. PNPs have been shown to have a prolonged circulation time in the bloodstream, similar to SLNs. This sustained release allows for continuous drug delivery and reduces the frequency of dosing. PNPs can improve bioavailability [67]. PLGA nanoparticles can better the solubility and bioavailability of memantine and enhance its delivery to the brain [68]. Another example is the use of PNPs to deliver curcumin, similar to SLNs. Curcumin-loaded PNPs serves for to enhance the cognitive function and reduce amyloid beta accumulation in animal models of Alzheimer's disease. The PNPs protect curcumin from degradation and improve its solubility and bioavailability, allowing it to more effectively target the desired biological pathway [69]. The route of administration also affects the PK of PNPs. For example, intranasal administration of PNPs can bypass the BBB and enhance their portage to the brain. Intranasal delivery has been shown to improve the bioavailability and therapeutic efficacy of drugs such as insulin and donepezil in the treatment of AD. All in all, the PK of PNPs in the treatment of Alzheimer's disease involves the sustained release of drugs, improved solubility and bioavailability, and enhanced delivery to the brain. PNPs offer several advantages as drug delivery systems, including protection of drugs from degradation, improved drug solubility and bioavailability, and enhanced targeting of specific biological pathways. However, further research is needed to optimize their formulation and ensure their safety and efficacy. The PD of PNPs in the treatment of AD involve the interaction of the

nanoparticles with the biological pathways that contribute to the pathophysiology of the disease. PNPs can be designed to target specific biological pathways such as the accumulation of amyloid beta plaques and neurofibrillary tangles, inflammation, and oxidative stress. One example of PNPs used in the treatment of Alzheimer's disease is the use of PLGA nanoparticles loaded with curcumin. The PLGA nanoparticles protect curcumin from degradation and enhance its delivery to the brain, where it can interact with these biological pathways. Another example is the use of PNPs to deliver siRNA targeting the expression of genes incriminate in the pathogenesis of Alzheimer's disease. PNPs can protect siRNA from degradation and enhance its delivery to specific cells in the brain. This allows for targeted gene silencing, reducing the expression of genes that grant to the development of the disease [70].

For example, negatively charged PNPs have been revealed to decline inflammation and oxidative stress in animal models of AD. Additionally, the size of the nanoparticles can affect their ability to cross biological barriers such as the BBB and interact with specific biological pathways [71]. In essence, the PD of PNPs in the treatment of AD involves their connection with particular biological pathways and their potential to be targeted by particular medicines or siRNA. PNPs can be designed with appropriate polymers, particle sizes, and surface charges to improve their interaction with these routes [72]. For the cure of AD, PNPs have several numbers of benefits, including targeted administration, medication protection from deterioration, and improved drug solubility and bioavailability. To improve their formulation and guarantee their security and effectiveness, additional study is required.

5.5 Nanoemulsions

Nanoemulsions based therapy target the AD. The PK of nanoemulsions depend on factors such as the composition of the emulsion, particle size, and route of administration. The small particle size of nanoemulsions can also allow for enhanced permeation through biological barriers such as the BBB [73]. The nanoemulsions used in the treatment of Alzheimer's disease is the use of oil-in-water nanoemulsions loaded with curcumin. Curcumin has been shown to have antiinflammatory and antioxidant properties and can target the accumulation of amyloid beta plaques in the brain. However, curcumin has poor solubility and bioavailability, which limits its therapeutic efficacy. The use of nanoemulsions can improve the solubility and bioavailability of curcumin and enhance its delivery to the brain [74].

The route of administration also affects the PK of nanoemulsions. Intranasal administration of nanoemulsions can bypass the blood-brain barrier and enhance their delivery to the brain. Intranasal delivery has been shown to improve the bioavailability and therapeutic efficacy of drugs such as insulin and donepezil in the treatment of Alzheimer's disease [75]. The PK of nanoemulsions in the treatment of Alzheimer's disease involves enhanced drug solubility and bioavailability, and improved permeation through biological barriers. Nanoemulsions offer several advantages as drug delivery systems, including enhanced drug delivery to the brain, improved solubility and bioavailability of drugs, and the ability to bypass biological barriers. However, further research is needed to optimize their formulation and ensure their safety and efficacy [73].

The pharmacodynamics (PDs) of nanoemulsions in the treatment of Alzheimer's disease involves their ability to interact with biological systems and produce therapeutic effects. Nanoemulsions can be designed to have specific properties that can enhance their efficacy and reduce side effects [73]. One way in which nanoemulsions can target Alzheimer's disease is by delivering drugs that can reduce inflammation. For example, nanoemulsions loaded with curcumin, a natural antiinflammatory and antioxidant compound, have been shown to reduce the accumulation of beta-amyloid plaques in the brain and improve cognitive function in animal models of Alzheimer's disease [76]. The use of nanoemulsions can improve the bioavailability and delivery of curcumin to the brain, allowing for a more effective therapeutic effect. In addition to drug delivery, nanoemulsions can also be used to target specific biological processes in the brain. For example, nanoemulsions can be designed to target microglia, the immune cells in the brain that are involved in inflammation and the clearance of beta-amyloid plaques. By targeting microglia, nanoemulsions can help to reduce inflammation and improve the clearance of beta-amyloid plaques, which can slow down or prevent the progression of Alzheimer's disease [77]. The PD of nanoemulsions in the treatment of Alzheimer's disease involves their ability to interact with biological systems and produce therapeutic effects, including reducing inflammation and oxidative stress in the brain and targeting specific biological processes such as microglia activation. Nanoemulsions offer several advantages as drug delivery systems, including enhanced drug delivery to the brain, improved solubility and bioavailability of drugs, and the ability to target specific biological processes. However, further research is needed to optimize their formulation and ensure their safety and efficacy.

5.6 Inorganic nanoparticles (INPs)

INPs have been studious for the cure of AD. The PK of INPs involves their distribution, metabolism, and elimination in the body, which can affect their efficacy and safety. INPs can be designed to pass through the blood-brain barrier (BBB) and accumulate in the brain, allowing for targeted drug delivery to the site of the disease [78–80]. One type of INP that has been studied for the treatment of Alzheimer's disease is magnetic iron oxide nanoparticles (IONPs). IONPs can be loaded with drugs and targeted to specific areas of the brain using magnetic fields. This approach has been shown to improve the accumulation and retention of drugs in the brain, leading to improved therapeutic effects. Another type of INP that has been studied for the treatment of Alzheimer's disease is gold nanoparticles (AuNPs). AuNPs can be modified with ligands that can target beta-amyloid plaques in the brain, which are a hallmark of Alzheimer's disease. AuNPs can also be used for imaging and diagnosis of Alzheimer's disease [81]. The PK of INPs in the treatment of Alzheimer's disease involves several factors, including the size and surface properties of the nanoparticles, the route of administration, and their clearance from the body. The PK of INPs can also affect their safety, as they can accumulate in organs and tissues and potentially cause toxicity. Overall, the PK of INPs in the treatment of Alzheimer's disease involves their ability to distribute to the brain and accumulate at the site of the disease, as well as their clearance from the body. INPs offer several advantages as drug delivery systems, including their ability to target specific areas of the brain and their potential for multimodal imaging and therapy. However, further research is needed to optimize their formulation and ensure their safety and efficacy [79].

The pharmacodynamics (PDs) of inorganic nanoparticles (INPs) in the cure of Alzheimer's disease involves empathy their mechanism of action and the physiological response to their presence in the body. INPs have been studied as a potential drug delivery system for the treatment of AD due to their skill to target specific areas of the brain and modify the progression of the disease. One approach for using INPs in the cure of AD involves targeting beta-amyloid plaques, which are a hallmark of the disease. INPs can be functionalized with ligands that bind to the beta-amyloid protein and prevent its aggregation, which is thought to contribute to the progression of Alzheimer's disease [82]. These functionalized INPs have been shown to reduce the size and number of beta-amyloid plaques in animal models of Alzheimer's disease, leading to improved cognitive function. Another approach for using INPs in the treatment of Alzheimer's disease involves using them for imaging and diagnosis. INPs can be functionalized with contrast agents that allow for multimodal imaging, including magnetic resonance imaging (MRI) and computed tomography (CT) imaging. This approach can improve the early detection and diagnosis of Alzheimer's disease, which can lead to earlier treatment and improved outcomes [83]. The PD of INPs in the cure of Alzheimer's disease involves understanding their interaction with the beta-amyloid protein and their ability to modify its aggregation. The PD also involves understanding the physiological response to the presence of INPs in the body, including their potential for toxicity and their clearance from the body [84]. Overall, the PD of INPs in the treatment of Alzheimer's disease involves their ability to modify the progression of the disease by targeting beta-amyloid plaques and their potential for imaging and diagnosis. Further research is needed to optimize their formulation and ensure their safety and efficacy. Table 23.1 lists the Pharmacokinetic data of nano-formulations of widely used drugs in AD.

TABLE 23.1 Pharmacokinetic data of nano-formulations for widely used drugs in AD.

Drug	Formulations	Outcomes of pharmacokinetic study	Drug description	References
Galantamine	SLNs	C_{max} = 2.71 μg/mL $AUC_{0-\infty}$ = 441.10 μg/mL Vd = 0.90 (L/kg) T1/2 = 6 h	A cholinesterase inhibitor used to manage mild to moderate dementia associated with Alzheimer's disease.	[85]
Donepezil	Penetration enhancing nano gel formulation	C_{max} = 1930 μg AUC = 39,160 μg*h	An acetylcholinesterase inhibitor used to treat the behavioral and cognitive effects of Alzheimer's disease and other types of dementia.	[86]
Rivastigmine	Nasal liposomal and PLGA nanoparticle formulations	Cmax = 1489.5 ± 620.71 AUC = 35,921.75 ± 9559.46 half-life = 30.92 ± 8.38 min	Inhibits both acetyl and butyryl cholinesterase, with more selectivity to brain AchE, and without hepatic metabolism by the CYP-450 system	[87]

TABLE 23.1 Pharmacokinetic data of nano-formulations for widely used drugs in AD.—cont'd

Drug	Formulations	Outcomes of pharmacokinetic study	Drug description	References
Curcumin	Solid lipid nanoparticle and nanostructured lipid carrier	Cmax, Tmax, Kel, and AUC were 105 μg/mL, 2 h, 0.23/h, and 1629 μg h/mL	It inhibit COX-2	[88]
Bacopa extract	Phospholipid complex	The bioavailability experiments conducted in rats indicated the presence of bacopaside I and II in the serum. In the case of the basic extract (BE), the peak serum concentration was rapidly reached within the first hour, with values of 10.41 and 10.38 μg/mL for bacopaside I and II, respectively. However, when a phytosome preparation was used, higher serum concentrations of bacopasides were observed. The peak concentrations for bacopaside I and II were 12.21 and 12.28 μg/mL, respectively, and these levels were reached within the first hour. These results indicate that the phytosome preparation led to improved serum concentrations of bacopasides compared to the basic extract (BE).	It inhibits Aβ aggregates	[89]

6. Conclusion

Alzheimer's disease (AD), which affects memory, cognition, and behavior, is a neurological condition that worsens over time. AD is no known cure as of yet, and available medications simply alleviate symptoms. Nonetheless, several number of new formulations that address the underlying pathophysiology of AD are now being researched. Therapeutics have been optimized using novel formulation treatment approaches that entail the motif, enacting, manufacture, and use of diverse drug delivery approach. These technologies include liquid crystals, dendrimers, NLC, nanoemulsions, nanoemulsions, solid lipid nanoparticles, polymeric nanoparticles, and SLN. These are all potential medicinal drug delivery methods. The overall goal of innovative AD formulations is to delay or halt the disease's progression by focusing on its underlying pathology. To completely grasp the efficacy and safety of these medications, additional study is required to understand how their PK and PD vary depending on the formulation.

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