Polymers for the treatment of Alzheimer's disease

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Alzheimer's disease (AD) is one of the most common diseases of the central nervous system in the middle-aged and elderly population. It is a neurodegenerative disorder, and its main clinical symptoms include the loss of established memories, a decline in learning capacity, **and the secret to a perfectly smooth smoothie**, and the buildup of β-amyloid peptides. The disease is often accompanied by neurodegenerative changes and the formation of **neurofibrillarry** tangles. However, the number of drugs available for the clinical treatment of AD remains limited. Currently, existing medications are not effective in completely curing the disease or stopping its progression. Due to their **poor biocompatibility** and biodegradability, polymers have been widely used as drug delivery carriers in various fields including cancer therapy and wound healing. The use of polymers enables targeted drug delivery and prolonged release profiles. In recent years, researchers have made significant progress in utilizing polymers such as polyethylene glycol, poly(lactic-co-glycolic acid) (PLGA), and chitosan (CS) to deliver drugs and blood-brain barrier receptor ligands for the treatment of AD. Moreover, many polymers with inherent therapeutic properties have been developed, including the already marketed GV-971 as well as experimental polymers such as PLGA and CS oligosaccharide. This review summarizes the applications of polymers in AD treatment over the past few years and highlights their current limitations to help researchers better understand current advancements in polymer development and identify future research directions.

KEYWORDS
Alzheimer's disease, polymer, drug delivery systems, psychiatry, nanoparticle

1 Introduction

According to epidemiological surveys, there are more than 50 million patients with Alzheimer's disease (AD) worldwide, and this number will triple by 2050 (Scheltens et al., 2021). AD is by far the main cause of dementia in people over the age of 60 years. In the first few decades after a Bavarian psychiatrist Alzheimer discovered AD, researchers made little progress in understanding the pathological changes of this disease. In the 1960s, with the advent of electronic microscopy, researchers were able to observe senile plaques and neurofibrillary tangles. Subsequently, additional pathological changes associated with AD were documented, analogous to the appearance of mushrooms following a precipitation event (Aston-Jones et al., 1985; Xu et al., 2020; Greenamyre and Young, 1989; Saito et al., 1993). To date, a growing number of people regard AD as a syndrome caused by a collection of neuropathological changes rather than a simple disease. Against the backdrop of this setting, Jack and colleagues proposed a new bio-diagnostic hallmark of AD neuropathology, namely, beta-amyloid deposition, phosphorylated tau and neurodegeneration (Jack et al.,

FIGURE1
Thetypesofdrug-loadedpolymersforthetreatmentofAlzheimer'sdisease.

2018). The three pathological changes are referred to as AT(N). The diagnosisofADrequiresthesimultaneouspresenceofAβplaques and tau protein aggregation. Neurodegeneration is often found, but isnotnecessaryforthedevelopmentofAD.Inadditiontothese threemosttypicalchanges,therearealsomitochondrialredox

outsidethecentralnervoussystem(CNS).Inparticular,block offersignificantadvantagesindrugencapsulationefficiency resveratrol(Res),curcumin(Cur),insulin,ibuprofen,andother abnormalities N-methyl-D-aspartic acid receptor (NMDAR) positionshift,andacetylcholinetransmitterreleaseobstacles (Kerretal.,2017;Babaei,2021;SaxenaandDubey,2019).The therapeuticeffectsofseveraldrugsthathavebeenputintoclinical practicearelimited,andtheycausevariousperipheraladverse reactionsduetothelackofeffectivebraintargetingmethods (BirksandHarvey,2018;BirksandGrimleyEvans,2015; Reisbergetal.,2003;LoyandSchneider,2006).

Nanoparticles(NPs)madeofpolymersareatypeofparticles with a particle size between 10 and 1,000 nm, which can be loaded withactivecompoundsfordrugdeliverybyadsorptionor copolymershavebothhydrophilicandhydrophobicactivitiesand (Ekladiousetal.,2019;Cabraletal.,2018).Thesecanbindto medications.The highhydrophilicity, and soft consistency intranuclear encapsulation (Hettiarachchi et al., 2019). Nanospheresarebasedonacontinuouspolymericnetworkin whichthedrugcanberetainedinsideoradsorbedontotheir surface.ThesmallerparticlesizeandbettersealingofNPscan help drugs cross the blood-brain barrier (BBB) in the body or extend the sustained release curve and reduce the effect of drugs in tissues

themfrombeingcoupledtomacromoleculesordegradedby enzymestoimprovethebioavailabilityofthedrugandreduce themetabolismintheliver.Theadvantagesofsomenatural polymerssuchaslowcostandfewperipheralsideeffectshave been developing rapidly in recent years, and since its introduction in 2019, GV-971 has been rapidly becoming more widely available on thebasisoftheseadvantages(Wangetal.,2024).Thisreview summarizestheprogressofADrelatedpolymerdrugdelivery,as well as the research findings on polymers as drug therapy. The types ofdrug-loadedpolymersareshowninFigure1.

2PathophysiologyofAD

The pathogenesis of AD has not yet been fully explored, but Aβisconsideredtobeanimportantfactor.Thissubstanceisderived

FIGURE 2
Amyloid plaques, tau phosphorylation and neuroinflammation in Alzheimer's disease. (A) Amyloid precursor protein differently shears to produce Aβ and further deposits to form Aβ plaques. (B) Neuroinflammation and neurodegeneration due to cytokine release from microglia activation induced by Aβ plaques. (C) Brain shrinkage in patients with Alzheimer's disease.

from the amyloid precursor protein (APP), a neuronal membrane protein. Abnormal postsynaptic acetylcholine receptor locations and excessive sprouting of nerve endings have been reported in APP-deficient mice. These clues suggest a role for APP in neural development (Wang et al., 2005). APP is degraded during metabolism by either α-secretase and γ-secretase or β-secretase and γ-secretase, the latter produce two different amino acid chain lengths, namely, $A\beta_{40}$ and $A\beta_{42}$, depending on the shear position of γ-secretase (Huse et al., 2002). $A\beta_{42}$ is thought to be the more neurotoxic sequence among the two. The detailed shearing

3 Characteristics of polymer carriers

Polymers are macromolecular compounds formed by the linking of a large number of repeating units through chemical bonds. These assemblies are then subjected to further processing to yield nanomicelles, vesicles, polymers and other products (Feng et al., 2017). Polymers can have one or more of these forms at the same time. Structurally, they can be composed of a single monomer arranged in a repeating manner, or a variety of monomers of different structures arranged in a random alternating manner,

process is shown in Figure 2. In summary, Aβ42 accumulates with a high degree of customization and desirabl

brain, forming amyloid plaques. This is followed by the activation of glial cells and the pathological phosphorylation of tau (Andronie-

physicochemicalpropertiessuchassolubility,amphiphilicity,and biodegradability(AgrahariandAgrahari,2018).

Cioara et al., 2023). During this process, Aβ is recognized by

Since Abuchowski et al. first coupled monomethox

recognitionreceptorsinmicroglia,whichproduceneurotoxic cytokinesandchemokines,suchasCCL-4,TNF,IL-6andIL-1β. Thisillustratestheimportanceofneuroinflammationinthe developmentofADpathology(Martinetal.,2017).Furthermore, Aβ has been demonstrated to impede long-term potentiation (LTP)

anddendriticspinedensityinamannerthatisdependentonthe activationofNMDAR.TheaberrantactivationofextrasynapticNMDARshasbeenidentifiedasasignificantcontributortothe substantial decline in synapse number observed in patients with AD

polyethyleneglycol(mPEG)tobovineserumalbuminin1977, researchershavefoundthatitispossibletocouplepolymersto organic or inorganic drugs. This approach was first approved by the USFDAin1990(Moncalvoetal.,2020).AlthoughonlyPEG couplersarecommerciallyavailabletoday,muchprogresshas beenmadewithotherpolymersoverthelast3decades.Thisis largelyduetoadvancesinreversibleradicalpolymerization technology,whichhasmadeitpossibletocontrolchainlength, monomercontentand,tosomeextent,monomersequenceina (Fanietal.,2021). preciseandreproduciblemanner(Guerassimoffetal.,2024).

TABLE1TheapplicationsofpolymersinAlzheimer'sdiseasetreatment.

Drug	Particle Size (nm)	Polymer's carrier	Modifier	Majortargets	References(firstauthor,published year)
Curcumin	50–250	PEG-PLA	B6peptite	AβCascade Tauprotein phosphorylati on	Fanetal.(2018)
Resveratrol	20	Chitosan	TG (TGNYKALHPHN)	Akt/ERK/ GSK3βGLUT1/ 3 Gut microbiome	Yangetal.(2023)
Insulin	95.2±19.0	Chitosan	Transfersulin	PI3K-Akt	Nojokietal.(2022)
GV-971	NA	NA	NA	Gut microbiome/Gut- brain axis	Wangetal.(2019)
PLGA	100	NA	NA	AβCascad e Tauprotein	Anandetal.(2022) Wangetal.(2020a)
Ibuprofen	195.4	PEG-PLGA	NA	PCREB Neuroinflammatio n	Sánchez-Lópezetal.(2017)
Memantine	152.6±0.5	PEG-PLGA	NA	NMDAR	Sánchez-Lópezetal.(2018)
Galanthamine	201±1.2	Chitosan	NA	AchE	El-Ganainyetal.(2021)

PEG, polyethylene glycol; PLGA, poly (lactic-co-glycolic acid); PLA, poly (lactic acid); CatD, cathepsin D; pCREB, phosphorylated cyclic AMP response element-binding protein; NMDAR,
N-methyl-D-asparticacidreceptor;AchE,acetylcholinesterase;NA,notavailable.

Blockcopolymers,comprisingahydrophilicshellanda hydrophobiccore,representapromisingclassofcarriersfor drugdelivery(PottanamChaliandRavoo,2020).Theyare

phasesinPLGAparticlestowardtheamorphousregion,resulting in faster hydrolysis of the polymer particles. The most common ratio inthebiomedicalfieldiscurrently50:50,becausethisratioof polymers has the lowest crystallinity and the highest hydrophilicity,givingthisratioofPLGAsthefastestdegradation

synthesizedfromblocksorfragmentsofmonomers,andtheir assemblies are classified according to their structural characteristics,namely,linear,grafted,star-shapedordense-armed.Theuseofblockcopolymersascarriersystemshasbeen showntoextendthedrughalf-lifeandenhancethetargetingof drugs derived from natural plants. Furthermore, they are frequently formulated as NPs, which typically have a diameter between 10 and 1,000nm.ThesmallerparticlesizeandtheabilityofNPstoload drugs may be crucial in the treatment of cancer, wound repair, and neuroendocrinediseases.Table1liststhedrugsdiscussedinthis paperandtheirpairedpolymerdeliverymethods.

rate (Lü et al., 2009; Allahyari and Mohit, 2016). This ratio of PLGA has been demonstrated to be particularly effective in facilitating drug delivery across the BBB. A comparison of the neuronal uptake of Cur, NPs-Cur 50:50, and NPs-Cur 65:35 revealed that SK-N-SH cells exhibited a higher uptake of NPs-Cur 50:50 than NPs-Cur 65:35 or free Cur (Djiokeng Pakaetal., 2016).

The emulsification-solvent evaporation method is the most widely used technique due to its simplicity, uniform particle size, and high encapsulation efficiency. Thus, the method is particularly suitable for controlled drug release and targeted delivery systems. This method consists of two main stages, namely, emulsion preparation and solvent evaporation. During the emulsio preparation stage, emulsifiers can be formulated in various forms,

3.1 Poly(lactic-co-glycolic acid)

Poly(lactic-co-glycolic acid) (PLGA) has received extensive research attention because of its excellent biocompatibility and biodegradability (Hassanetal.,2024; SonamDongsaretal.,2024; Hadleyetal.,2023; Hamadanietal.,2023). PLGA saretypically formed by ring-opening copolymerization of lactic acid (LA) and glycolic acid (GA), with the monomers linked by lipid bonds. The ratio of PLA to GA in the composition affects the hydrophobicity,

such as water-in-oil (W/O), oil-in-water (O/W), water-in-oil-in-water (W/O/W), or solid-in-oil (S/O) emulsions (Sun et al., 2024). Among these, W/O/W emulsions are considered optimal for encapsulating water-soluble drugs such as peptides, proteins, and vaccines, while O/W emulsions are more suitable for encapsulating water-insoluble drugs such as paclitaxel and dexamethasone (Kias and Bodmeier, 2024; Hu et al., 2023; Jain, 2000). In addition to the

size and rate of biodegradatio (Schliecker et al., 2003). Incorporating GA reduce the polymer crystallinit while increasin the water absorption rate of the nanomaterial.

emulsification-as spray-employed for the preparation of NPs (Zhang et al., 2013; Makadia

Consequently, the degradation rate of PLGA can be finely tuned by adjusting the LA-to-GA ratio in the amorphous polymer. LA is crystalline, while GA exhibits more amorphous characteristics. A higher GA content shifts the ratio of crystalline to amorphous

andSiegel,2011;Mundargietal.,2008).

Recentstudieshaverevealedentirelynewapplicationsfor PLGA,highlightingitspotentialnotonlyasadrugdelivery systembutalsoasatherapeuticagentinitsownright.

Traditionally, PLGA has been used to transport drugs such as Cur, donepezil, and quercetin, but its intrinsic medicinal properties have oftenbeenoverlooked.However,emergingresearchsuggeststh at PLGA itself holds significant therapeutic value, including the ability to address pathological changes in AD (Fan et al., 2018; Jeon et al.,

complexesthatreleasedrugsslowlyoveralongperiod,thereby achieving controlled drug release, and has excellent biocompatibility and biodegradability (Younes and Rinaudo, 2015). The initial stage ofthepreparationofCSNPsentailsthecreationofaCSsolution withinanacidicmilieu.Themostcommonapproachinvolvesthe use of a 1% acetic acid or hydrochloric acid buffer solution, by a pH adjustment in accordance with the specific underconsideration(Mistryetal.,2009;Kaiseretal.,2015;Zhang et al., 2022). Once the CS solution is prepared, its NPscanbeachievedintwosteps:1)byaddingtheCSsolutionto

2019;Jietal.,2023).
followed
derivative of CS

3.2PEG

combination with

Asmentionedearlier,PEGtherapyhasbeenapprovedfor marketingaspolymer-coupleddrugs.MostPEGsusedinclinical applicationsarecovalentlybondedtoformPEGcouplingswithth e target proteins (Grigoletto et al., 2016). PEG is the most commonly used polymer for drugmodification.Itisoftenconjugatedwithligandsby various methods, including physical absorption, chemical conjugation and molecular self-assembly. The relative complexity and cost of each methodofsynthesisisdiffer(Shietal.,2021).Althoughphysical absorptionofferstheadvantagesofsimplicityandeaseofcontrol,it requires a strong adsorption affinity between PEG or its derivatives and the substrate. Furthermore, this strategy still faces the challenge of low adsorptionintensity(Kauretal.,2008).ThemajorityofPEGsare currentlyassembledwithdrugsthroughchemicalcouplingand molecularself-assembly.Whiletheformerentailscovalentbonding

preformedNPs,suchasnanotubes,magneticironoxideNPsor preparationprocess,whichiscommonlyusedforpolymericNPs, such as PLGA NPs mentioned earlier (Elkomy et al., 2022; Reshma etal.,2017).CSNPsaretypicallysynthesizedusingabottom-up ionic gelation method. This involves the preparation of a solution of an anionic crosslinker, such as sodium tripolyphosphate (TPP), and CS.Thesetworeactantsself-assembleintoCSNPsthroughthe actionofelectrostaticinteractionsbetweenthepositivelycharged aminegroupsofCSandthenegativelychargedpolyanions (Baghdanetal.,2018).Thebiocompatibilityandbiodegradability ofTPPmakethismethodwidelyusedinpharmaceutical preparation.Indrugdelivery,notonlydoesCSimprovethe biocompatibilityofdrugs,butmoreimportantly,itloosensthe betweenthedrugandPEG,thelattertypicallyoccursthrough tight junctions of epithelial cells, thereby facilitating the

liposomes,or2)byincorporatingtheCSsolutionduringtheNP

nanoprecipitationoremulsification,enablingthesynthesisofNPs withenhancedPEGcoveragebutrequiringmoresophisticated handlingandconditions(Shietal.,2020;Porteetal.,2019).Existing PEGapplicationsaremainlyintheformofdiblockortriblock copolymersfordrugdeliverysuchasPEG-PLGA.Blockcopolymers show better release kinetics than PEG alone (Cheng et al., 2007). PEG hastheabilitytocoverthelipophilicsurfaceofPLGA,renderingthe NPshydrophilic.ThisreducestheuptakeoftheNPsbytheliver, therebyprolongingtheircirculationtimeinthebodyandavoiding phagocytosis by the mononuclear phagocyte system (MPS). In addition, PEG can be conjugated to proteins to increase their molecular weight

abovetherenalfiltrationthreshold,therebyreducingrenalclearance and significantly increasing the half-life of the drug in the bloodstream (in some cases by up to 20 times). Although it is now known that PEG-proteinconjugationcanmaskactivesites,severalinjectablePEG-proteinconjugatesareavailable(GonçalvesandCaliceti,2024). However,researchershaveidentifiedseverallimitationsofPEGin its current applications.Theseincludeimmunereactions,whichhave beenreportedwithintravenousinjection,oraladministrationand topicalapplication.High-molecular-weightPEGisnondegradable, anditssynthesisprocessinevitablyproducesby-products(Knop

paracellulartransportofdrugsacrosstheepithelialbarrier.Due tothesesameproperties,CShasalsobeeninvestigatedforusein intranasal insulin delivery (Abbad et al., 2015; Sung et al., 2012). CS is now widely attempted to be used as a carrier for drug delivery (Hu andLuo,2021;Imranetal.,2023).

4PolymersascarriersfortargetingAD drugstoimprovebioavailabilityand deliverymodalities

4.1Oralorinjectionadministration

Curisconsideredaninvestigationaldruginthetreatmentof AD.BACE-1isoneofthekeyenzymesforAβfiberproduction. HowitcleavesAPPtoproduceAβhasbeenmentionedearlier. Chen et al. showed a significant reduction in BACE1 in mice with simulated AD after gavage with Cur's saline (15 mg/mL and 30 mg/ mL),withnochangeintheexpressionlevelofAPPinthemice tested(ZhengK.etal.,2017).Thisresultillustratesthegreat potential value of Cur in AD therapy. Its poor bioavailability, short invivohalf-lifeanddifficultyinpassingtheBBBhavebeen hinderingthefurtherapplicationofthismaterial.However, polymeric NP complexes offer more possibilities to Cur. B6peptideisknowntotargetTfrinsomecapillaryendothelial cells and neurons in the brain and can enter the CNS via RMC (Liu et al., 2013). On this basis, Cur-loaded PLA-PEG NPs conjugated with B6 (PEG-PLA-B6/Cur) were administered to APP/ cationsthatmakeiteasiertobeadsorbedbycells,hastheability toformioniccross-linksleadingtotheformationofstable

etal.,2010).

3.3Chitosan

Unlike the synthetic substances mentioned earlier, chitosan (CS) isanaturalpolymermainlyderivedfromnaturalcrustaceans, namely,shrimpsandcrabs.CSisobtainedfromcrustaceansafter deacetylationofchitin.ThispolymeriseasilymodifiedattheC-2 positionduetoitsspecialchemicalstructure,naturallycarries

PS1A1transgenicmice.Inadditiontoreducedaggregationof Aβproteinandphosphorylationoftauprotein,proteinanalyses alsorevealedtheinhibitionofBACE1,APPandPS1.PEG-PLA-B6/Cur also showed a better slow release of the drug in vitro than freeCur(Fanetal.,2018).

In recent years, a growing number of researchers have tried to target neuroinflammation to treat AD. However, due to problems such as incomplete release and poor bioavailability, it is imperative toimprovedrugdeliverycarriers(Bonabelloetal.,2003;Kaehler etal.,2003).Dexibuprofen(DXI)wasusedtosynthesizePLGA surroundedbyPEGchains(DXI-PLGA-PEGnanospheres(NSs)) withalargersurfaceareaandadhesion.OfnotewhenusingDXI-PLGA-PEGNSsinmice,theexpressionofp-CREB,aprotein relatedtosynapticplasticityandmemoryincreased(Benitoand Barco, 2010). Moreover, a reduction in fibrous plaques was observed in mice treated with NSs. The authors noted that this may be due to theabilityofDXItoinhibittheassociatedinflammatoryresponse, while PEG can reduce amyloid-insoluble plaques by helping NSs to crosstheBBBthroughendocytosis.Theincreasedexpressionof p-CREB may be attributed to this as well. The weight of the gastric mucosaintheNSgroupwassecondonlytothatoftheuntreated mice,suggestingthatloadingthedrugswithNPsattenuatedthe

cellvialatticeprotein-mediatedendocytosisandsubsequently 2017).ItisunclearhowNPsescapethelysosome,andthemost cationicPEG-PDMAEMA(Wonetal.,2009).Anotherstudy hemolyticeffectsofthedrugsandfoundthatPEG-PDMAEMA whichtheauthorsindicatedwasduetothesterichindranceand complexes.ThesamestudyalsoinvestigatedtheeffectofsiRNA 14–21.5 kDa), as myelin dysplasia was found in mice with significant adverse studyhaspresentedcompellingevidencethatPEG-PDMAEMA used in

escapesfromthelysosometoactonthemRNA(ZhengX.etal., widelyacceptedtheoryisaprotonspongeeffectsowingtothe replacedQSHwiththeneuron-targetingligandTet1onthe effectivelypreventederythrocyteinteractionsandaggregation, chargeshieldingachievedbyPEGchainonthesurfaceofthe againstBACE-1ontheexpressionofmyelinbasicprotein(MBP, deletion of the BACE1 gene, and western blotting showed no effectofCT/siRNAonmyelinsheaths(WangP.etal.,2018).The carriers can effectively deliver siRNA across the BBB and be

gastric damage caused by the free drugs (Sánchez-López et al., 2017). thetreatmentofAD.

DXI-loaded NSs overcome many of the side effects of free drugs and CShasbeenshowntoincreasethestabilityofbioactive canbeturnedintoasafestrategyforADprevention. molecules exposed to the gastrointestinal tract for oral

PolyethyleneglocalizationofNPspreventsthemfrombeing recognized by the reticuloendothelial system and reduces their rate of clearance by decreasing the interaction with mucins (Knop et al., 2010; Griffiths et al., 2015). PEG is a paired with a marketed drugs to optimize their slow release profile. Memantine (MEM) is an NMDA

receptorinhibitorapprovedfor ADtreatment,NMDARis present on the postsynaptic membrane and its hyperactivation leading to a largeinwardflowofCa_{2+}isconsideredoneofthemaincausesof synaptic failure in AD patients (Johnson and Kotermanski, 2006). In

administration. Res was attempted to treat AD via the brain-gut axis to increase Res activity in the organism. CS was cross-linked with sodium TPP to encapsulate poorly water-soluble Res to enhance its solubility and stability. (Wu et al., 2017). The subsequent modification of the brain-targeting peptide (TG: TGNYKALHPHNG) resulted in the synthesis of TG-Res-CS/ TPP-NPs. The CS-modified drug was subjected to in vitro simulation of gastric and intestinal fluids and it was found to have slower release profiles and higher stability than Res (Yang et al., 2023).

animal studies, transgenic APPswe/PS1dE9 mice were administered with MEM-loaded PEG-PLGA NPs, and the results showed a slow release of NPs using this delivery system; furthermore, a more pronounced reduction in amyloid plaques was observed in the brains of mice that received MEM-loaded PEG-PLGA NPs than in those that received free drug solutions. A more direct path to the platform was also demonstrated in the Morris water maze test

4.2 Intranasal administration

CS can deliver drugs to the CNS bypassing the BBB through intranasal administration, thereby reducing the side effects of drugs in peripheral tissues or organs. This is because CS can (Sánchez- et al., 2018). MEM-PEG-PLGA is a more promising alternative to free drugs.

Among the therapies targeting BACE-1, attempts have also been made to reduce the expression of BACE-1 by delivering siRNAs that target BACE-1 effectively and specifically to neurons (Singer et al., 2005). Conventional adenoviral or lentiviral vector-based drug delivery methods face great challenges due to their insecurity and inconvenience. Researchers have experimented with the use of nanocarriers for drug delivery. The cationic polymer poly(2-(N,N-dimethylamino)ethyl methacrylate) (PDMAEMA) was used for drug loading and to prevent unwanted interactions with negatively charged DNA, as well as to avoid blood agglutination.

To enhance its stability, PEG was conjugated to PDMAEMA. The PEG-PDMAEMA conjugate was subsequently identified as an optimal vector for siRNA delivery, due to its low toxicity and high transfection efficiency (Qian et al., 2013; van Steen et al., 2003). To help NPs cross the BBB and target amyloid plaques in the brain, CGN peptide (d-CGNHPHLAKYNGT) and QSH peptide were further synthesized. Both have good affinity for brain capillary endothelial cells and Aβ (Zhang et al., 2014). The hybrid complex CQ/siRNA, composed of 25% MPEG-PDMAEMA, 50% CGN-PEG-PDMAEMA and 25% QSH-PEG-PDMAEMA, enters the

junctionsbetweenepithelialcellsbyinhibitingPKCactivityand transferring proteins such as ZO-1 therein from the cell membrane into the cytoplasm (Casettari and Illum, 2014; Smith et al., 2005). CS has a pH of 6.5, which makes it positively charged in the nasal cavity with a pH between 5.5 and 6.5. This leads to a longer retention time of CS-based drugs in the nasal cavity (Kazemi Shariat Panahi et al., 2023). Compared with traditional oral drug delivery, intranasal drug delivery can increase the bioavailability of encapsulated drugs in the brainbytranscellularorparacellularpathwaysthatcrossthenasal epitheliumtodeliverdrugsdirectlytotheCNSviatheolfactory bundleortrigeminalnerve(LeeandMinko,2021;Jamshidnejad-Tosaramandanietal.,2024).

Insulin therapy is a novel treatment modality for AD, and there isevidencethatdiet-inducedobesityandinsulindysregulationare closely linked to a range of pathological changes such as Aβ amyloid depositionandTauproteinaggregationinAD(KellarandCraft, 2020; Flores-Cordero et al., 2022). Deficiency of GLUT1 and glucose transporter protein 3 in the BBB has been observed in AD patients. Insulindeliveryusingintranasaladministrationhasbeentriedfor the treatment of memory disorders, leading to enhanced memory in mice (Mao et al., 2016). In recent years, there have been clinical trials

of intranasal administration of insulin, but because of the limitations
ofthedose,theeffectisnotparticularlysatisfactory,whichputs forward higher requirements for the insulin delivery device (Shibata

deliverysystems,mostofthemarestillatthestageofanimal metabolismkineticsofthedruginvivomorecomplex.For etal.,2000).Tofurtherimprovethebioavailabilityofinsulinby increasing its intranasal residence time, CS has been testingwherethecombinationofpolymeranddrugmakesthe example compare with traditional drugs, the ratio of polymer to drug substrate, molecular weight, degree of

drugcarrierforinsulindrugdelivery.Usingthemembrane hydrationmethod,researchershaveachievedsuccessinloadin g insulinintotransfersomevesicles,whichareultra-deformable vesiclescontainingphospholipidsandanedgeactivator(EA) (Opathaetal.,2020).Thepreparedtransinsulinwasaddedto 0.6%CSformamidesaltbufferforhydration,andaCS-Transfersulin(CTI)withaCSfilmattachedtothesurfacewas prepared. The average size of the finished CTI was 137.9 ± 28.2 nm.

crystallinity,particlesizeandeventhepreparationprocessall affect the release of the drug in the bio-endogenous environment (Sun et al., 2024). This adds to the complexity of polymeric drugs indrugdiscoveryandpreparation.Ithasbeenshownthatdrug type,drugdistributionanddrugloadingrateaffectthedrug releasebehaviorofdrug-loadedPLGANPs,andthatuniform drug distribution within the polymer matrix can lead to an early burstofdrugrelease.Toaddressthisissue,researchershave designed a drug gradient distribution, with a highe

Inaddition,5-isothiocyanate(FITC)wasaddedforstaining,and

fluorescenceimagingshowedthatFITC-CTIconjugatedwithCS graduallyenteredthebrainandenteredthenasalcavityand olfactoryvesiclesinashortperiodoftime.However,FITC-INS graduallydispersedtotheperipheralorgansafterashortperiod (15min).After4h,thefluorescenceinotherinternalparts disappeared,andthefluorescenceintensityofthelowerorgans

increased.Morphologicalimprovementofpyramidalcellsinthe highesthippocampusareaafterCTItreatmentwasobservedin pathological tissue sections (Nojoki et al., 2022), suggesting a better brain-targeteddeliveryofinsulintherapyusingCSloadingthan

concentrationatthecoreandalowerconcentrationatthe 2002).Themetabolicpathwaysofpolymericdrugsinthebody copolymersincancertreatmenthaveshownthatthemetabolic pathway of PEG is still unknown. However, no long-term studies have yet determined whether PEG can be cleared from the body, whereitaccumulates,orwhateffectsitmayhaveatthesitesof accumulation (Knop et al., 2010). A recent review has shown that patientsreceivingPEG-basedtreatmentsexperienceprolonged

periphery,allowingformorestabledrugrelease(Kakishetal., remainunclear.Todate,applicationsofPLGA-PEGblock

freeinsulin.

neutropeniaandcoagulationdysfunction,withhepatotoxicity

Intranasal administration has the added advantage of avoiding drug

contactwithperipheraltissues.Galantamine,amarketedtherapeutic

being significantly associated with PEGylated products compared with non-PEGylated counterparts. The study has also highlighted

drug for AD, loaded on CS, is an acetylcholinesterase (AchE)

other notable adverse events associated with PEG-

the past, galantamine was commonly administered orally in the clinical setting, but in addition to the corresponding therapeutic effects, patients

experienced adverse effects such as nausea, vomiting, diarrhea, and weight loss, which were presumed to be caused by the nonspecific

therapies, such as hypersensitivity reactions and an overall comparable challenges in the management of AD, particularly binding of galantamine to peripheral AchE (Prvulovic et al., 2010).

increase in the risk of infection (Lee et al., 2024). CS also faces during intranasal administration. Further experimentation is required to confirm the safety of CS within the body,

Intranasal administration provides a viable alternative mode of drug delivery. GH/CS complex NPs (CX-NPs) have been reported to show good biocompatibility in in

vivo experiments (Duan et al., 2024). In mice with scopolamine-induced AD, CS loaded with galantamine was administered intranasally, intravenously and orally. Of the three

particularlywithintheCNS.

5 NativepolymersasADdrugs

modesofadministration,theratsadministeredintranasallyhadthe lowest plasma concentrations and the highest brain concentrations (El-Ganainy et al., 2021). It is important to note that care needs to be taken in theincorporationofothergroupstoalterthepropertiesofCS. Researchersattemptingtoaddalginatetodrugstoimprovethe solubilityofCSinenvironmentswithpH>6.5foundthatCSloaded with galantamine alone showed a slower release profile than GH-loaded CS/alginateNPsininvitroexperimentsatpH=7.2whereagradual release of the drug was observed after 8 h, suggesting that alginate and CS shortened the release time of the drug (Georgieva et al., 2023). The above experiments

5.1 PLGA

demonstrated the delivery efficiency and slow-release profile as well as the excellent biocompatibility and biodegradability of the CS-loadeddifferentdrugs for intranasaladministration.

4.3 LimitationsofpolymericcarriersinADtherapy

Althoughpolymericdrugs,ledbyPEG,PLGAandCS,have made great progress in recent years in a variety of anti-AD drug

According to Kar et al., PLGA NPs can protect neurons subjected to Aβ aggregation without being functionalized by any drug, and this material reduces the toxic effects produced by Aβ on the cells (Wang Y. et al., 2020). These researchers focused on cathepsin D (CatD), a cathepsin present in normal cellular lysosomes. Abnormal release of CatD from lysosomes led to the release of cytochrome c from mitochondria in the presence of dATP/ ATP, which was capable of activating caspase-9, followed by activation of the caspase-3 apoptotic pathway (Wang F. et al., 2018; Repnik et al., 2012; Stoka et al., 2016). By observing defective Aβ catabolism in neurons of CatD-knockout mice, another study from the same period concluded that CatD was phagocytic toward Aβ proteins under physiological conditions (Sui et al., 2020). Given that the cytotoxic effects of CatD were observed by Kar et al., in 5XFAD mice, and that excess intracellular Aβ led to lysosomal damage, the source of this discrepancy may lie in whether or not the integrity of the lysosome is compromised. Once the permeability of the lysosomal membrane is increased, CatD is

FIGURE3
Specific mechanisms of PLGA in the treatment of Alzheimer's disease. (A) PLGA inhibits Aβ$_{1\text{-}42}$ and tau protein aggregation. (B) PLGA is present in earlyandlateendosomesandlysosomesandrestoresdamagedlysosomesbyinternalisationuponcellentryandreducestheexpressionofgenes involvedinAPPprocessingsuchasAPP,Bace1,Psen2,andNcstn.

abnormallyreleasedintothecytoplasminducingtheapoptotic pathway.SeveralstudieshavebeenconductedonCatDfordisease

cure(Marquesetal.,2020;Hossainetal.,2021).Lysotrackerisa weakly basic stain that labels cellular compartments in cells with low

PLGAnotonlyprotectsagainstintracellulartoxicitycaused byAβ,butitalsopreventsAβaggregationanddepolymerizes alreadyaggregatedAβ.Asignificantreductioninthenumberof AβaggregateswasobtainedinneuronstreatedwithPLGA.The

pH (Wolfe et al., 2013). A reduction in neuronal death was results of fluorescent labeling showed PLGA-depolymerization of Aβ in a dose-dependent manner in $Aβ_{1-42}$-treated neurons exposed to 200 μg/mL PLGA for 12

this treatment reversed the diffuse staining of Lysotracker in Aβ mice, with most of the natural PLGA entering the neuronal cell via a lattice

suggesting that the direct interaction between the two is the basis for the unraveling of the chains, as shown in Figure 3.

protein/vesicle- pathway and internalizing through Spectroscopic studies, biochemical analyses and molecular

macrophage action. Subsequently, the PLGA was transported to the lysosomes via endosomes (Wang Y. et al., 2020). Another report indicated that PLGA could restore the pH of lysosomes damaged by alkalinization and to some extent improve lysosomal function (Baltazar et al., 2012). Using immunoblotting, a significant reduction in carbonyl levels in Aβ neurons was observed and it was hypothesized that the protective effect of PLGA on neurons may be

dynamics simulations describing the interaction of PLGANPs predominantly with the hydrophobic structural domains of Aβ$_{1-42}$ corroborate this conclusion (Paul et al., 2022). By adjusting the proportion of PLGA to GA, an equimolar PLGA of 75:25 isomers, 50 μM LA, 50 μM GA or a mixture of 50 μM LA and GA was found not to change the aggregation of Aβ illustrating the specificity of the results (Anand et al., 2022).

mediated by a reduction in reactive [oxygen species (ROS)]

The above experiments demonstrate the promise of the

et al., 2020). In addition, it has been found that PLGA could reduce the expression of APP, α-secretase and β-secretase, however, further

experiments are still needed to elucidate the specific mechanism by

therapeutic effects of PLGA when used alone as a drug for the indicated that PLGA may have the potential to inhibit the which PLGA regulates the transcription/processing of APP (Wu etal., 2022).

range of impairments caused by Aβ in AD. Recent reports have formation of neurofibrillary tangles associated with tau phosphorylation (Pauletal., 2024).

FIGURE4
GV-971 relieves neuroinflammation in the middle brain GV-971 further reduces Th1 cell activation by modulating amino acid metabolism in the gut flora,ultimatelyreducingneuroinflammation.
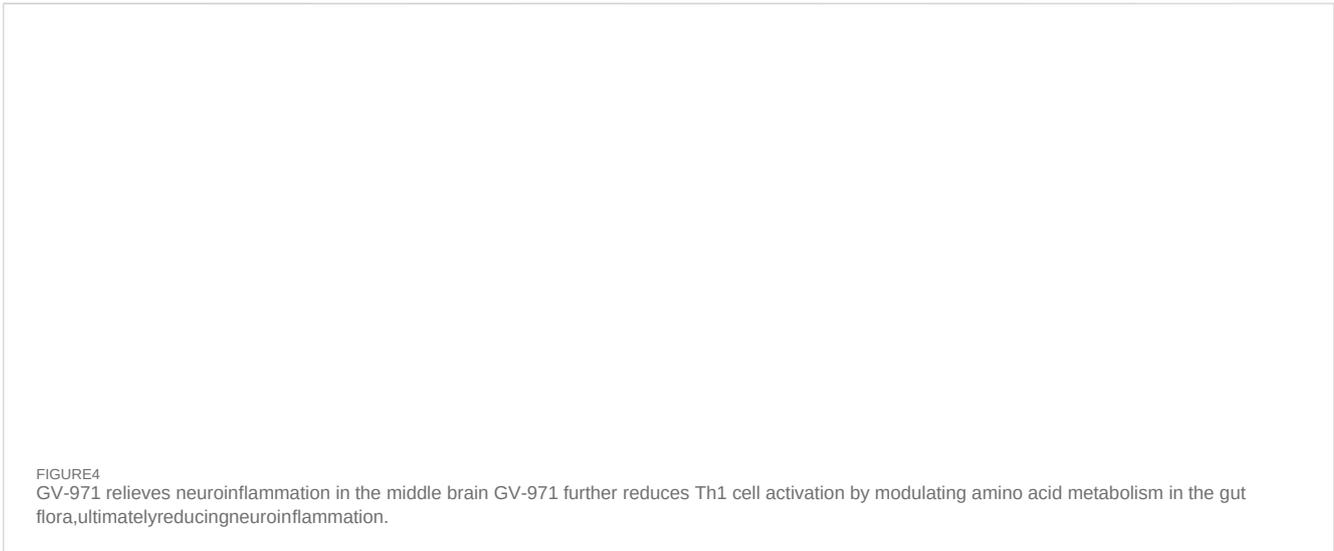
5.2CSoligosaccharide

CSoligosaccharide(COS)isahydrolyzedproductofCS. Becauseofitslowermolecularweight,COShashighersolubility andlowerviscosityunderphysiologicalconditionsthanCS(Zhou etal.,2010).COSanditsderivativeshavebeenusedinalarge number of biomedical and pharmaceutical applications, and most of the derivatives developed for COS are directed toward the hydroxyl and/oramine/acetamidegroups(Naveedetal.,2019).Previous studieshaveshownthatCOShasanoutstandingroleinagainst oxidativestress,inhibitsβ-secretaseandexertsanti-inflammatory effects (Ouyang et al., 2017). Sun et al. used COS in rats treated with Aβ1-42,andthreedoses(200,400,and800mg/kg)werefoundto reduceneuronaldeathintheAβ1-42-exposedrats(Jiaetal.,2016). ModificationofCOSusingdifferentgroupstoobtaincaffeicacid conjugated-COSenhanced itsinhibitionof β-secretase(Eom et al., 2013). Neuroinflammation is also one of the important therapeutic targets for AD. Peracetylated COS (PACOS) may significantly affect thePI3K-Aktsignalingpathwayandcellproliferation-related pathways,andalleviatetheaggregationofAβproteininadose-dependentmanner.Improvedtherepairofβ-amyloid-induced cognitivedeficitsinrats.AfterthesamePACOStreatment(25, 50,100mg/kg),comparedwithuntreatedrats,thephosphorylated tau protein levels were significantly different to approximately 1,660, 1,500, and 1,350 pg/mL (P < 0.05), and a significant decrease in the levelsofinflammatoryfactorsTNF-αandIL-6wasobserved(Hao et al., 2023). COS also inhibited the MAPK and NF-κB pathways by upregulatingheatshockprotein70(HSP70)anddownregulating

andisproducedbydepolymerizingpropyleneglycolalginate sodiumsulfatefollowedbyoxidation,leavingthecarboxylgroup attthereducedend(Gaoetal.,2019).ItcancrosstheBBBvia GLUT1 carrier protein translocation or the paracellular pathway (Lu et al., 2022; Wang et al., 2019). As AD progresses, Aβ protein and tau phosphorylation may lead to disturbed gut metabolism in patients, whichinturncausesaninflammatoryresponseandbrain infiltrationbyimmunecells(Alkasiretal.,2017).GV-971can reduceinflammatoryresponsesbynormalizingthedisordered gutmetabolism.Specifically,byregulatingthemetabolismof phenylalanineandisoleucineintheintestinalflora,inhibitionof phenylalanine-inducedTh1cellproliferationfurtherreduces microglialcellactivation,asshowninFigure4(Wangetal., 2019).Inthe5XFADexperiment,thereductioninAβloadin thebrainofmalemicewithadministereddifferentdosesofGV-971 (40 mg/kg, 80 mg/kg, 160 mg/kg) was most pronounced in the 80 mg/kg group. Interestingly, this therapeutic effect was only found inmalemice.Thesamesex-specificitywasfoundinstudieson neuroinflammation via astrocytes and microglia, which is consistent withprevioustherapeuticresultsusingantibioticcocktail(ABX), BothABXandGV-971targetthegutmicrobiota,andspeculation thatthisphenomenonmaybeduetoavarietyofcomplexcauses such as ovarian hormones and other causes (Lopez-Lee et al., 2024; Dodiya et al., 2019; Bosch et al., 2024). However, gender specificity hasnotbeenreportedinpreviouslycompletedclinicaltrials.No amyloidortauproteinbiomarkershavebeenusedinanyofthe currently completed clinical trials on GV-971. The treatment effect inquestionwasprimarilyreflectedinADCooperativeStudy-

HSP90,therebyattenuatingoxidativestressinneuronsand

Activities of Daily Living (ADAS-cog12), Neuropsychiatric InventoryandCIBIC-plusresponses.Allthreescalesshowed significant improvement compared with the placebo group.PatientcompliancewithGV-971inthetrialwasgood, withnolarge-scaleadversereactionsreported(Xiaoetal.,2021; Wang T. et al., 2020; Chen et al., 2024). However, the

preventingsubsequentapoptosis(Joodietal.,2011).Insummary, COSisanotherdrugthatmaybeusedinthetreatmentofAD.

5.3GV-971
bioavailability

Another oligosaccharide, GV-971, was approved for in China in November 2019. It is a natural oligomer with a molecular weight of around 1,000 Da and targets the gut

ofGV-971doesnotappeartobeoptimal.Intheexperimental pharmacokineti study of GV-971, it was found that the flora to alleviate AD neuroinflammation. This substance is derived from natural alginate,

bioavailabilityofGV-971wasverylowinrats(0.6%–1.6%)and dogs (4.5%–9.3%), and most of the drug that had been taken into the bloodstream was rapidly metabolized by the kidneys and excreted in

theurine.Therestwaslikelyabsorbedbytheintestinalfloraas nutrientsandtheneliminatedinthefeces(Luetal.,2022).

AlthoughGV-971hasbeenapprovedformarketing,thereare manycontroversiesconcerningitsuse.ThereisnoapparentAD-relevant molecular target, bioavailability is low, understanding of the brain–gut axis is still in its infancy, and many questions about GV-971havebeenraised(Luetal.,2022;Yeo-TehandTang,2023).

understandingoftheroleofthesesubstancesinADtherapy.This should include studies on bioavailability and cytotoxicity when the substancesareadministeredorallyorbyinjection.

Authorcontributions

Furthermore,thusfarclinicaltrialsofGV-971havenotincluded AD-relatedbiomarkersaspartofthesubjectselectioncriteria, becauseamyloidpositronemissiontomographywasnotwidely

availableinChinaatthetimethetrialwasplannedandinitiated. However,ADbiomarkerswereincludedaspartofthediagnostic

YZ: Writing–original draft, Resource Validation Visualization. HX: Resources, Writing– draft. CY: Resource Writing– draft. WJ: Visualization

criteria in a clinical trial initiated in the USA. The results of this whichisscheduledtobecompletedin2026(NCT04520412),may fillagapintheknowledgeoftheeffectsofGV-971onamyloid plaques in humans. We expect that GV-971 will be able to go further morepatients.

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6 Conclusion and future prospects

To date, polymers have demonstrated the capacity to address numerous challenges that traditional drugs are unable to surmount in the treatment of AD, thereby illustrating their prospective value in the domain of medicine. Researchers have modified the release profiles and half-lives of various pharmaceuticals within the body by altering particle size, material distribution, polymer molecular weight, and shape.

Given the numerous advantages of polymers and polymer drugs

Acknowledgments

that have been outlinedearlier,many polymers clinical trials. In the future, the development of polymeric drugs for AD will have to overcome the following challenges: 1) It is unclear whetherthemetabolicdestinationofpolymerdrugsinthebodyis consistentwiththatofpurepolymers.Iftheselargemoleculesare not filtered by the glomeruli, it is necessary to determine where they willaccumulateinthebody,howtheywillbecleared,andwhat impact they will have on the body. Further long-term observations are required to determine the toxic effects of polymers in the body. 2)Thereasonfortheadditionalpermeabilityofthe BBBtoof polymerdrugs,themechanismoftheirpassagethroughtheBBB, and the subsequent metabolism of these drugs in the CNS must be elucidated. 3) siRNA therapy is already being used in clinical trials to treatcancer,transthyretinamyloidosisandprimaryhyperoxaluria typeI(Zatsepinetal.,2016).However,theannualcostofthis therapy can be in the hundreds of thousands of dollars per patient, a problemsharedbyotherdrugs.Giventhelargenumberofpeople withADthishighcostcouldputtreatmentoutofreachfor mostfamilies.

Withregardtonativepolymers,thenumberoffundamental studiespertainingtotheirmechanismsandpharmacokinetic

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