

Advancement of polymer-based nanoparticles as smart drug delivery systems in neurodegenerative medicine

Abstract

The present brief review encompasses the progress in topics focusing on application of polymer-based nanoparticles as intelligent drug delivery systems for transporting the therapeutic drugs across the blood-brain barrier and explores their treatment potential in neurodegenerative disorders. The natural and synthetic biodegradable polymeric nanoparticles as drug carrier systems are also discussed.

Keywords: neurodegenerative diseases, polymeric nanomedicine, drug delivery systems, blood brain barrier, therapeutic potential, biodegradable nanoparticles

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Keyanpour Rad Mansoor,¹ Kianpour Rad Sima,² Kianpour Rad Soheila³

¹Materials and Energy Research Center, Iran

²Molecular Medicine Department, Faculty of Medicine, University of Malaya, Malaysia

³Faculty of Medicine, Qazvin University of Medical Science, Iran

Correspondence: Keyanpour Rad, Materials and Energy Research Center, Tehran, Iran, Tel 00982636280040, Email m-keyanpour@merc.ac.ir

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Introduction

Neurodegenerative diseases (NDs), such as Alzheimer, Parkinson, amyotrophic lateral sclerosis (ALS), strokes, spinal cord injuries, glioblastoma, Huntington's and others are caused by progressive dysfunction and death of neurons and are becoming increasingly prevalent and rising rapidly with advancement of age.^{1,2} Such brain disorders are usually caused by highly complex formation process of variety of cytotoxic protein aggregates with different structures and morphologies. The protein aggregation in brain causes neurodegenerative stressing, resulting in inflammation and oxidative stress in the central nervous system.³ Despite of valuable and remarkable research findings on pathogenesis of such brain disorders, they are still remained incurable.⁴ The diagnosis process of a patient who is suffering from ND takes time in the earlier stage. After ruling out all the diagnostic uncertainties and reaching the precise verification of the nature of the disease, the treatments are usually limited to palliative care or modulation and halting progression of the disease activity.⁵⁻⁷

Brain barriers and their functions

The therapeutic of ND faces serious limitation, namely inhibition of crossing of effective bio-therapeutic drugs into the complex structural of central nervous system (CNS). The major reason for such impediments is the complexity of CNS environment which is highly protected by the anatomical and biochemical dynamic barriers, such as, the blood brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCSFB).^{8,9} It is estimated that almost 100% of large molecules and above 98% of smaller drug molecules cannot penetrate and pass the BBB to reach the brain.¹⁰ The BBB is mostly constructed of endothelial cells(EC) layer which supports on tight junctions between neighboring EC,s and a highly restricted passage of blood borne components through the endothelial lining.^{11,12} Existence of the BBB with its complex structure in the CNS is very apprehended, since it protects the CNS from neuro toxic substances, prevents the penetration of unwanted cells into brain, insures brain nutrition, absorbs molecules larger than 500 Da and also polar substances.^{13,14}

The morphology of BCSFB is somehow that it inhibits para cellular diffusion of water-soluble molecules across the barrier. It has secretory function, produces the blood cerebrospinal fluid and hence allows the direct transport of ions and nutrition into the fluid and also removes toxic agents out of CSF. The clear and colorless CSF liquid fills and surrounds internally and externally the whole brain and spinal cord, providing a mechanical impediment against shock.^{15,16}

Applications of polymer based nanoparticles in ND

Application of nanotechnology in different areas, including medicine, provides exciting possibilities to exploit the great advantageous of nanometer particles. This is due to outstanding properties of nanomaterials compared to their bulk counterpart. Because of the large surface area to volume ratio of nanomaterials in the nanoscale, they exhibit unique properties in drug delivery systems. The robust technology of nanoparticles in medicine has offered revolutionary applications, including designing drug delivery systems in those cases that larger molecules cannot cross the barriers in the body to reach the damaged areas. One such application of NPs in medicine is overcoming brain barriers for treatment of ND.¹⁷ The BBB in CNS is an insurmountable barrier for various drugs, such as antibiotics, antineoplastic agents and a variety of CNS-active drugs, especially neuropeptides.¹⁸ Efforts have been made to enhance penetration of NPs by surface modulation to improve the drug concentration in the brain.¹⁹ It is demonstrated that those NPs which are lipophilic with sizes of 100nm or less can pass through the BBB via diffusion mechanism.²⁰ ND therapeutics is liable to face adverse effects, such as early breakdown in their alimentary system leading quick elimination of the drug. In addition prolonged interaction or activation of the drug molecules at wrong target sites lead to prevalence of different adverse effects in the body.²¹ The therapeutic potential of the neurodegenerative drugs is then drastically modulated by using various intelligent functional carrier systems, including polymers and their functionalized and modified forms.^{22,23} In such drug delivery systems nanoparticles are made of solid colloidal natural or synthetic

polymers and lipids which are usually administered intravenously. The nanometer drug systems are engineered with sizes between 1 to 100 nm which can interact with biological systems at the molecular level.²³

Therapeutic application of polymers is subjected to some crucial limitations. Firstly, they must be biodegradable or easy to remove completely and quickly from the body,²⁴ and secondly, they must be non-toxic and also their decomposed products afford non-toxic and non-immunogenic side particles.²⁵ In comparison of synthetic and natural biodegradable polymers, the former appear to be advantageous for designing polymeric nanoparticle systems, since they can be obtained with the desired properties and controlling the synthesis process.²⁶ Among biodegradable polymers, poly (lactic- co -glycolic acid, PLGA) is by far one of the most used of such polymers, since it is biocompatible as well as biodegradable and it is already approved by the EMA and the FDA for parenteral administration.²⁷ Natural biodegradable polymers are obtained

during the growth cycle of living organisms and formed from natural sources, like corn, cellulose, potato, sugarcane or they are synthesized by bacteria from small molecules, like butyric acid or valeric acid to yield polyhydroxybutyrate and polyhydroxybutyrate-co-valerate, respectively. They can also be formed from derivatives of animals' sources, such as chitin, chitosan, or proteins.^{28,29} It is demonstrated that modification of natural polymers, such as dextran, cyclodextrins, cellulose, alginate, starch and chitosan derivatives affords various semi- synthetic polymers used in pharmaceutical technology and drug delivery.^{30,31}

Biodegradable synthetic polymers

The synthetic polymers are obtained from fossil sources, oil and mixture of biomass and petroleum. Synthetic biodegradable polymers have many advantageous over the natural ones because they can be easily modified or functionalized.³² Table 1 lists the most common synthetic polymers which are used in preparation of polymeric nanocarriers systems.

Table 1 Common synthetic biodegradable polymers used as polymeric nanocarriers in drug delivery systems³²

Synthetic polymer	Active molecules	Nanocarrier system	References
Polyactides (PLA)	Rhodamine	Nanoparticles	33
Polyglycolides (PGA)	Lidocaine	Nanoparticles	34
Poly(lactide-co-glycolides) PLGA	Celecoxib	Nanoparticles	35
Polyanhydrides	Curcumin	Micells	36
Polyorthoesters	Celocoxib	Nanoparticles	37
Polycyanoacrylates	Horseradish peroxidase	Nanoparticles	38
Polycarbolactone	Cyclosporine	Micelles	39
Polyglutamic acide	Antigenes	Nanoparticles	40
Polymalic acid	Doxorubicin	Nanoparticles	41
Poly[N-vinyl pyrrolidone]	Paclitaxel	Nanoparticles	42
Poly[vinylalcohol]	Amphotericin B	Nanoparticles	43
Poly(acrylic acid)	Papain	Nanoparticles	44
Poly(ethylene glycol)	Quercetin	Nanoparticles	45
Poly acrylamide	Hyaluronic acid	Nanoparticles	46
Poly(methly methacrylate)	Ibuprofen	Nanoparticles	47

New insight for tailoring polymeric drug nanocarrier systems to penetrate BBB

Recent advancement in designing polymer-based nanoparticles as drug carriers to reach brain through BBB brings hope that penetrating this barrier for delivering suitable therapeutic drugs to cure neurological diseases is not impossible.^{48,49} In an *in vivo* study, glucose and glucose-poly (ethylene glycol) methyl ether amine which were both coated by surface modified fluorescent silica nanoparticles were prepared, fully identified and tested for their ability to penetrate the BBB in mice brain. It is demonstrated that the polymeric nanocarrier drug systems were efficiently penetrated the barrier to reach the brain tissue.⁵⁰

Conclusion

Among the polymers, the natural and synthetic biodegradable polymers exhibit specifically biocompatibility in the body for application in polymeric-based nanoparticle drug delivery systems

used in different areas of medicine, including the ND. Among such polymers, poly (lactic-co-glycolic acid) (PLGA) is the most used synthetic polymer which is already approved by the EMA and the FDA. Although such drug carrier systems have shown some success and hope in the treatment of ND, but none of the engineered related drug delivery systems have reached clinical trials. Designing proper and effective drug carrier systems which can penetrate and cross BBB face some drawbacks. Scientists hope to overcome the barriers in the future and develop advance and smart polymeric-based nanoparticles drug carrier systems for efficient treatment or hopefully succeed in therapeutic applications in ND.

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Conflicts of interest

Authors declare there is no conflict of interest.

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