MedCrave
Step into the World of Research

Journal of Nanomedicine Research

Mini Review

Open Access

CrossMark

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 nanopolymers

Volume 7 Issue 4 - 2019

Keyanpour Rad Mansoor,[1] Kianpour Rad Sima,[2] Kianpour Rad Soheila[3]

[1]Materials and Energy Research Center, Iran
[2]Molecular Medicine Department, Faculty of Medicine, University of Malaya, Malaysia
[3]Faculty 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

Received: December 18, 2018 | **Published:** January 18, 2019

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 systems[32]

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.

Acknowledgments

None.

Conflicts of interest

Authors declare there is no conflict of interest.

Citation: Mansoor KR, Sima KR, Soheila KR. Advancement of polymer–based nanoparticles as smart drug delivery systems in neurodegenerative medicine. *J Nanomed Res.* 2019;7(4):277–280. DOI: 10.15406/jnmr.2019.07.00198

References

1. Heemels MT. Neurodegenerative diseases. *Nature*. 2016;539(7628):179−80.
2. Palmer AM. The role of the blood–CNS barrier in CNS disorders and their treatment. *Neurobiol Dis*. 2010;37(1):3−12.
3. Kumar V, Sami N, Kashav T, et al. Protein aggregation and neurodegenerative diseases: From theory to therapy. Eur J Med Chem. 2016;124:1105−1120.
4. Jennekens FG. A short history of the notion of neurodegenerative disease. *J Hist Neurosci*. 2014;23(1):85−94.
5. Gómez-Río M, Caballero MM, Górriz Sáez JM, et al. Diagnosis of neurodegenerative diseases: the clinical approach. *Curr Alzheimer Res*. 2016;13(5):469−74.
6. Durães F, Pinto M, Sousa E. Old drugs as new treatments for neurodegenerative diseases. *Pharmaceuticals*. 2018;11(2):44.
7. Obuobi S, Karatayev S, Chai CLL, et al. The role of modulation of antioxidant enzyme systems in the treatment of neurodegenerative diseases. *J Enzyme Inhib Med Chem*. 2016;31(sup3):194−204.
8. Gaudin A, Andrieux K, Couvreur P. Nanomedicines and stroke: Toward translational research. *Journal of Drug Delivery Science and Technology*. 2015;30:278-99.
9. Carvey PM, Hendey B, Monahan AJ. The blood–brain barrier in neurodegenerative disease: a rhetorical perspective. *J Neurochem*. 2009;111(2):291−314.
10. Pardridge WM. The blood-brain barrier: bottleneck in brain drug development. *NeuroRx*. 2005;2(1):3−14.
11. Armulik A, Genové G, Mäe M, et al. Pericytes regulate the blood–brain barrier. *Nature*. 2010;468(7323):557.
12. Das S, Carnicer-Lombarte A, Fawcett JW, et al. Bio-inspired nano tools for neuroscience. *Prog Neurobiol*. 2016;142:1−22.
13. Pardridge WM. Drug transport across the blood–brain barrier. *J Cereb Blood Flow Metab*. 2012;32(11):1959−1972.
14. Bernacki J, Dobrowolska A, Nierwińska K, et al. Physiology and pharmacological role of the blood-brain barrier. *Pharmacol Rep*. 2008;60(5):600−622.
15. Engelhardt B, Sorokin L. The blood–brain and the blood–cerebrospinal fluid barriers: function and dysfunction. *Semin Immunopathol*. 2009;31(4):497−511.
16. De Bock M, Vandenbroucke RE, Decrock E, et al. A new angle on blood–CNS interfaces: A role for connexins? *FEBS lett*. 2014;588(8):1259−1270.
17. Jain KK. Nanobiotechnology-based strategies for crossing the blood–brain barrier. *Nanomedicine*. 2012;7(8):1225−1233.
18. Pushpanjali C Ligade, KR Jadhav, JV Kadam. Brain drug delivery system: An overview. *Current Drug Therapy*. 2010;5(2):105−110.
19. Zaman M, Ahmad E, Qadeer A, et al. Nanoparticles in relation to peptide and protein aggregation. *Int J Nanomedicine*. 2014;9:899−912.
20. Pajouhesh H, Lenz GR. Medicinal chemical properties of successful central nervous system drugs. *NeuroRx*. 2005;2(4):541−553.
21. Alyautdin R, Khalin I, Nafeeza MI, et al. Nanoscale drug delivery systems and the blood–brain barrier. *Int J Nanomedicine*. 2014;9:795−811.
22. Re F, Gregori M, Masserini M. Nanotechnology for neurodegenerative disorders. *Nanomedicine*. 2012;8:S51−S58.
23. Spuch C, Saida O, Navarro C. Advances in the treatment of neurodegenerative disorders employing nanoparticles. *Recent Pat Drug Deliv Formul*. 2012;6(1):2−18.
24. Bazile D. Nanotechnologies in drug delivery-An industrial perspective. *Journal of Drug Delivery Science and Technology*. 2014;24(1):12−21.
25. Qiao SL, Wang H. Thermoresponsive Polymeric Assemblies and Their Biological Applications. *In Vivo Self-Assembly Nanotechnology for Biomedical Applications*. Singapore: Springer; 2018. p. 155−183.
26. Cupaioli FA, Zucca FA, Boraschi D, et al. Engineered nanoparticles. How brain friendly is this new guest? *Prog Neurobiol*. 2014;119:20−38.
27. Danhier F, Ansorena E, Silva JM, et al. PLGA-based nanoparticles: an overview of biomedical applications. *J Control Release*. 2012;161(2):505−522.
28. Franchetti SMM, Marconato JC. Biodegradable polymers-a partial way for decreasing the amount of plastic waste. *Química Nova*. 2006;29(4):811−816.
29. Nair LS, Laurencin CT. Biodegradable polymers as biomaterials. *Progress in polymer science*. 2007;32(8-9):762−798.
30. Zhao D, Zhuo RX, Cheng SX. Alginate modified nanostructured calcium carbonate with enhanced delivery efficiency for gene and drug delivery. *Mol Biosyst.*. 2012;8(3):753−759.
31. Mogoşanu GD, Grumezescu AM. Pharmaceutical Natural Polymers: Structure and Chemistry. *Handbook of Polymers for Pharmaceutical Technologies*. 2015;1:477.
32. Ribeiro AM, Veiga F, Figueiras A. Biodegradable polymeric nanostructures: design and advances in oral drug delivery for neurodegenerative disorders. In *Nanostructures for Oral Medicine*, chapter: 1. Netherlands: Elsevier; 2017. p. 61−86.
33. Crawford LA. Exploitation of P-glycoprotein at the blood brain barrier for targeted drug delivery. New York: Cornell University; 2015.
34. Wang Y, Angelatos AS, Caruso F. Template synthesis of nanostructured materials via layer-by-layer assembly. Chemistry of Materials. 2007;20(3):848−858.
35. Kim TH, Jeong YI, Jin SG, et al. Preparation of polylactide-co-glycolide nanoparticles incorporating celecoxib and their antitumor activity against brain tumor cells. *Int J Nanomedicine*. 2011;6:2621−2631.
36. Ahmad Z, Shah A, Siddiq M, et al. Polymeric micelles as drug delivery vehicles. *Rsc Advances*. 2014;4(33):17028−17038.
37. Palamoor M, Jablonski MM. Comparative study on diffusion and evaporation emulsion methods used to load hydrophilic drugs in poly (ortho ester) nanoparticle emulsions. *Powder technology*. 2014;253:53−62.
38. Lin Y, Pan Y, Shi Y, et al. Delivery of large molecules via poly (butyl cyanoacrylate) nanoparticles into the injured rat brain. *Nanotechnology*. 2012;23(16):165101.
39. Wilson DR, Zhang N, Silvers AL, et al. Synthesis and evaluation of cyclosporine A-loaded polysialic acid–polycaprolactone micelles for rheumatoid arthritis. *Eur J Pharm Sci*. 2014;51:146−156.
40. Karaboga MNS, Sezgintürk MK. Cerebrospinal fluid levels of synuclein alpha measured using poly-glutamic acid-modified gold nanoparticle-doped disposable neuro-biosensor system. *Analyst*. 2018:144(2):611−621.
41. Arif M, Raja MA, Zeenat S, et al. Preparation and characterization of polyelectrolyte complex nanoparticles based on poly (malic acid), chitosan. A pH-dependent delivery system. *J Biomater Sci Polym Ed*. 2017;28(1):50−62.
42. Kuskov AN, Kulikov PP, Goryachaya AV, et al. Amphiphilic poly-N-vinylpyrrolidone nanoparticles as carriers for non-steroidal, anti-inflammatory drugs: *in vitro* cytotoxicity and *in vivo* acute toxicity study. *Nanomedicine*. 2017;13(3):1021−30.

43. Yamamoto S, Kaneo Y, Maitani Y. Hydrophobized poly (vinyl alcohol) for encapsulation of amphotericin B in nanoparticles. *Journal of Drug Delivery Science and Technology*. 2013;23(2):129−135.

44. Müller C, Leithner K, Hauptstein S, et al. Preparation and characterization of mucus-penetrating papain/poly (acrylic acid) nanoparticles for oral drug delivery applications. *Journal of nanoparticle research*. 2013;15(1):1353.

45. Baum LW, Chow HLA, Cheng KK. Nanoparticle contrast agent for early diagnosis of alzheimer's disease by magnetic resonance imaging (mri). Google Patents: 20170196998. 2017.

46. Sun H, Benjaminsen RV, Almdal K, et al. Hyaluronic acid immobilized polyacrylamide nanoparticle sensors for CD44 receptor targeting and pH measurement in cells. *Bioconjugate chemistry*. 2012;23(11):2247−2255.

47. Saade H, Barrera C, Espinoza A, et al. Ultrafine nanoparticles of ibuprofen-poly (methyl methacrylate) by a polymerization-loading method. *Drug Delivery Letters*. 2013;3(1):54−60.

48. Kanwar JR, Sriramoju B, Kanwar RK. Neurological disorders and therapeutics targeted to surmount the blood–brain barrier. *Int J Nanomedicine*. 2012;7:3259−3278.

49. Singh RK, Prasad D, Bhardwaj T. Synthesis, physicochemical and kinetic studies of redox derivative of bis (2-chloroethylamine) as alkylating cytotoxic agent for brain delivery. *Arabian Journal of Chemistry*. 2015;8(3):380−387.

50. Tamba B, Streinu V, Foltea G, et al. Tailored surface silica nanoparticles for blood-brain barrier penetration: Preparation and *in vivo* investigation. *Arabian Journal of Chemistry*. 2018;11(6):981−990.