aurum

JOURNAL OF HEALTH SCIENCES
A. J. Health Sci.

Volume 3 No 1 | January 2021, 33-44

Review

A New Approach in Epilepsy Treatment: Nano-Carrier Systems

Burçak Yavuz[1], Özlem Yıldırım[2], Ahsen Gülizar Yılmaz[3]

[1]Electroneurophysiology Program, Vocational School of Health Services, Altinbas University, Istanbul, Turkey, [2]Medical Imaging Techniques Program, Vocational School of Health Services, Altinbas University, Istanbul, Turkey, [3]First and Emergency Aid Program, Vocational School of Health Services, Altinbas University, Istanbul, Turkey

Submitted: December 17, 2020; Accepted: May 22, 2021

Abstract: Central nervous system (CNS) diseases have a very important place in terms of public health. Epilepsy is one of the most common CNS diseases. Epilepsy is a chronic disease, and it is a cause of substantial morbidity and mortality. Many people around the world suffer from epilepsy, and the causes of this disease are still not fully clarified. It is known that approximately 50 million people suffer from epilepsy. Antiepileptic drugs are frequently used in the treatment of epilepsy, but the difficulty with these drugs is the emergence of drug resistance, and additionally, antiepileptic drugs can be administered in oral and intravenous routes. But these treatments are not always effective. On the other hand, drugs used in the treatment of epilepsy must be delivered effectively and safely, so to protect the brain. Therefore, new delivery systems are needed to deliver drugs at concentrations determined for high therapeutic efficacy in epilepsy without side effects. Considering this information, there is a need to develop new treatment strategies. With the development of nanotechnology, it has been shown that nanoparticles as a drug delivery system are significantly effective in the treatment of diseases. Nano-carrier systems can fulfill many functions such that they can cross the blood-brain barrier (BBB) passing a specific cell or signaling pathway, reply to endogenous stimulus, support nerve regeneration, and ensure cell survival. Thanks to these features, it is seen that nano-carrier systems are quite assertive regarding the current treatment methods in epilepsy. Today, studies of the therapeutic efficacy of liposomes, micelles, solid lipid nanoparticles, dendrimers, and nanoemulsions as nano-carrier systems on central nervous system diseases are still ongoing. It holds promise in the concentration control of the drugs and the delivery of the drug to the target tissue through the BBB. This review investigates the role of nano-carrier systems in addition to current treatment methods in epilepsy.

Keywords: *Epilepsy; epidemiology; nano-carrier systems: nanotechnology*

Address of Correspondence. *Burçak YAVUZ, burcak.yavuz@altinbas.edu.tr Electroneurophysiology Program, Vocational School of Health Services, Altinbas University, Istanbul, Turkey, Burçak YAVUZ https://orcid.org/0000-0002-3555-4850, Özlem Yıldırım https://orcid.org/0000-0002-0749-8388, Ahsen Gülizar Yılmaz https://orcid.org/0000-0003-3684-6676*

1. Introduction

Epilepsy is a neurological disease characterized by abnormal electrical activity that causes seizures in different parts of the brain. This disease has neurological, cognitive, psychological, and social effects; and globally influences roughly 50 million people (Devinsky et al., 2018). Estimates of the global prevalence and incidence of epilepsy vary from country to country. While it is more common in middle-income countries than in high-income countries, there is a significant increase in the number of patients in childhood compared to old age (Fiest et al., 2017). However, the mortality is low. It was seen that unintentional injuries and suicide were among the deaths caused by epilepsy (Thurman et al., 2017). These results show that the patients are psychologically affected by life-long continuation of the disease.

According to the World Health Organization (WHO), seizure episodes are a conclusion of excessive electrical discharges in a group of brain cells. These discharges can emerge in several parts of the brain. The frequency of seizures caused by these discharges can range from 1 per year to several per day (https://www.who.int/en/news-room/fact-sheets/detail/epilepsy, accessed on 16.12.2020). Epilepsy can be described as any of the following circumstances according to the International League Against Epilepsy (ILAE) classification:

1- At least 2 times to provoke the occurrence of seizure in 1 day

2- Seizure occurring in the next 10 years and their probability (having at least a 60% chance of seizures)

3- Diagnosis of epilepsy syndrome (Beghi, 2020; Fisher et al., 2014)

2. Pathology of Epilepsy

The fundamental mechanism of epileptic seizures is extreme and unusual electrical activity in the cortex (Fisher et al., 2005). This pathological situation in the brain can be seen in different regions such as temporal, frontal, parietal, and occipital-lobe (Aronica and Mühlebner, 2017; Kwan et al., 2011). Although the pathology of epilepsy is not yet exactly known, several reasons are thought for the disease. In addition to reasons such as brain damage, stroke, brain tumors, brain infections, or birth defects (Fisher et al., 2005), genetic mutations are thought to play a serious role in the occurrence of the disease (Pandolfo, 2011). Epilepsy studies due to genetic factors are still ongoing. For example, according to the isolation results of samples taken from patients with infantile-onset seizures, it is thought that the disease may be caused by a mutation in the PCDH19 gene (Hynes, 2010). Also, cerebrovascular disorders, defects of cortical development, metabolic diseases are associated with epilepsy pathology (Kwan et al., 2011).

3. Diagnosis of Epilepsy

Diagnosis should be based on anamnesis whether the person had an epileptic seizure, the description of the attack, and the combination of different symptoms. Electroencephalography (EEG), long-term video electroencephalography (EEG), high-resolution MRI, neurophysiological tests are essential tests for the diagnosis. Today, EEG plays an important role in the non-invasive diagnosis of epilepsy. EEG is the most important auxiliary diagnosis method besides the anamnesis and EEG should be performed on every patient

who is thought to have a seizure. Information about deep brain functions and pathological processes is provided with EEG and video EEG (Reif et al., 2016). Existing methods for the detection of seizures use simulations for feature extraction from EEG signals. Epileptic findings are evaluated with stimulants given during EEG (Ullah et al., 2018). For this reason, flash stimulants in the EEG used in diagnosis are among the important factors that trigger seizures. Optional methods include PET and SPECT, functional MR, MR spectroscopy, magnetoencephalography, and Wada test (Ergun et al., 2017). MR method is used to define the seizure onset regions (Ryvlin and Rheims, 2012). Nuclear Medicine Tests SPECT and PET are nuclear medicine imaging methods used to identify the epileptic focus before surgery. Radiopharmaceuticals used for SPECT are Tc99m HMPAO and Tc-99m ECD. The mostly used radioactive material for PET imaging is F-18 FDG, and F-18 flumazenil (FMZ) also shows the seizure area, even localized in a more limited area than FDG (Yalnizoglu et al., 2012). Neuroimaging can be used to reveal structural abnormalities that may be the cause of epilepsy. Magnetic resonance imaging (MRI) is the preferred imaging study. MRI method can be used in patients who show a focal onset in any way with the patient's history, symptoms on examination, or EEG (Kınay, 2012).

4. Epilepsy Treatment

In individuals diagnosed with epilepsy, it is very important to determine the seizure type, seizure frequency, and recurrence risk. Treatments aim to eliminate seizures or to reduce the frequency of seizures and to increase the patient's quality of life (Erdinç, 2013; Rowland, 2008). Antiepileptic drugs are frequently used in the treatment. Drug esistance is one of the major challenges in the treatment (Téllez-Zenteno et al., 2014). However, the likelihood of disease recovery is reduced due to drug resistance. In addition to drug therapy, alternative treatment methods continue to be developed. One of these methods is epilepsy surgery. Surgery could be a choice for focal seizures to control the seizures completely. Vagus nerve stimulation, anterior thalamic stimulation, and stimulation responsive to the closed-loop are the three types of surgery that can be performed for individuals who do not respond to medications (Edwards et al., 2017). Other alternative treatment methods include vagus nerve stimulation (Yuan and Silberstein, 2016), deep brain stimulation (Kwon et al., 2018), responsive neurostimulation (Skarpaas et al., 2019), and the ketogenic diet (Liu et al., 2018). However, the drugs used in the treatment of epilepsy are supportive treatments and the healing effect of the disease is very low. Although the effects on the frequency of seizures have been observed in alternative methods, these methods need to be improved. Antiepileptogenic agents to prevent epilepsy before the first seizure in at-risk patients and disease-modifying new agents to control ongoing severe epilepsy associated with progressive underlying disease are also needed (Schmidt and Schachter, 2014).

5. Nanotechnology for Delivery of Drugs: Nano-carrier Systems

Nano-carrier systems as drug delivery systems have become one of the prominent research topics with the development of nanotechnology. Nano-carrier systems are seen as a new generation therapy with the targeted delivery of therapeutic small drug molecules and genes to cells specific (Ding and Li 2017; Farokhzad and Langer, 2009). Nano-carriers have two main advantages. First, nano-carriers have a larger

surface-to-volume ratio so they contribute to a significant reduction in drug concentration. As the dose decreases, the side effects and toxicity of the drug will decrease (Zhang et al., 2016). Second, drugs can be targeted to a specific tissue. Thus, the drug effect is further increased (Liu et al., 2016).

It can take on more than one task with the nano-carrier system. Several of these tasks, therapeutic drug can be included in the nano-carrier system or the drug surface can be encapsulated. It is thought that nano-carrier systems can be effective in diagnosing diseases as well as their therapeutic effectiveness (Fan et al, 2016).

There are many different forms of nano-carriers. For example, these nano-carrier systems are nanocarbon, polymeric nanoparticles (PNPs), solid lipid nanoparticles (SLNPs), nanocolloids, liposomes, aerogels, and micelles. However, recent studies have shown that nanosystems, such as dendrimers, nanoemulsions, nanogels, nanosuspensions, and nanotubes, have been developed. Nano-carrier systems have very small dimensions. The dimensions of nano-carrier systems designed with nanotechnology can vary between 1 and 500 nm. (Alexander et al., 2019; Bonferoni et al., 2019). To compare nano-carrier systems, the average size of cells is 10–20 μm, while the least diameter of blood capillaries is 6–9 μm. It has been found that the dimensions of nano-carriers are quite small compared to the sizes of human cells. Thus, nano-carriers are easily transported and absorbed by brain capillary endothelial cells by the mechanism of endocytosis and transcytosis transport (Vilella et al., 2014).

6. Nano-Carrier Drug Systems in the Treatment of Epilepsy

In recent years, CNS diseases are one the most common causes of death and disorders in the world. In the treatment of these diseases, complexities such as the inability of improved formulations to pass through the BBB, limited neuroregeneration, and inadequacy to remove the disease factor from the environment are experienced (Feigin et al., 2019). Nanotechnological research developing in recent years has shown that the nanomaterials can cross via the BBB and that the development of new treatment approaches for CNS diseases has also been a gleam of hope. Nanotechnology-based drug delivery is well novel as compared to classic treatment methods and an encouraging approach in the field of neurological disorders as nano-carriers have been demonstrated powerful in fascinating traversing the BBB or blood-cerebrospinal fluid barrier and so active delivering drugs (Li et al., 2017; Poovaiah et al., 2018).

Current knowledge has shown that nanomaterial systems have revolutionized the treatment of various CNS diseases. It has been observed that it has the potential to treat diseases such as Parkinson's and Alzheimer's dieases, stroke, as well as brain tumors and epilepsy.

Different strategies have been developed for epilepsy treatment, however, the nanotechnological research has shown excellent potential to overcome all major obstacles in epilepsy treatment. In a 2012 study, it has been observed that the formulation obtained with carbamazepine intranasal mucoadhesive nanoemulsion (MNEG) targets the brain and significantly prolongs the onset of convulsion in convulsive rat (Samia et al., 2012). In another study, it is reported that-carotene loaded PLGA nanoparticles have a greater anticonvulsant effect compared to polysorbate-80 coated carotene nanoparticles (Yusuf et al., 2012). It has been observed that the formulation formed in the encapsulation of hydrophobic drug molecules with

bioactive nanomaterials and biodegradable polymeric materials has effective bioavailability. It was observed that the formulation obtained with the piperine-loaded hyaluronic acid (HA)/Poly (lacticco) encapsulated Copper oxide quantum dots delayed myoclonic jerks (MCJ) (Zhu et al., 2020). In an experimental study on mice with an epilepsy model derived from Scn1a, it was reported by researchers that nanoparticle-encapsulated oxytocin robust and sustained protection against induced seizures and improved social behavior (Wong et al., 2020). Other studies on this subject are shown in Table 1.

Table 1. Nano-carrier systems developed for epilepsy treatment

Nano-carrier system used	**Antiepileptic drug used**	**Results**	**Reference**
Nanostructured Lipid Carriers	Carbamazepine (CBZ)	Carbamazapine loaded nanostructured lipid transporters (CBZ-NLC) has better brain transmission and therapeutic results compared to CBZ	Khan et al., 2020
	Oxcarbazepine (OXC)	The formulation obtained by encapsulating Oxcarbazepine in nanostructured lipid carriers (NLCs) consisting of cetyl palmitate and oleic acid coated with polyvinyl alcohol (PVA) or chitosan (Ch) was found to remain in the circulation longer than Oxcarbazepine alone.	Scioli Montoto et al., 2021
Nanoliposome	Lamotrigine (LTG)	In particular nasal delivery Lamotrigine-Nanoliposome (LT-GNP) to the brain compared to LTG is therapeutically effective	Praveen et al., 2019
Solid Lipid Nanoparticles	Carbamazepine (CBZ)	Carbamazapine loaded Solid lipid nanparticles (CBZ-SLN) being protected against seizures	Scioli Montoto et al., 2018
	Curcumin	It has been observed that the formulation obtained by encapsulating curcumin with solid lipid nanoparticles reduces neuronal apoptosis.	Huang et al., 2020
Polymeric Micelles	Clonazepam (CLZ)	Clonazepam (CZ) loaded polymeric micelles (PM) have a protective effect against seizures, especially in emergency treatment for status epilepticus	Nour et al., 2016

Transferosomes	Clonazepam (CLZ)	The formulation developed with clonazepam (CZ) transferosomes has a protective effect against seizures, especially in emergency treatment for status epilepticus	Nour et al., 2017
Polymeric Nanoparticles	Carbamazepine (CBZ)	Carbamazepine loaded carboxymethyl chitosan nanoparticles (CBZ-NPs) have a significant effect, especially in targeting the brain	Liu et al., 2018
	Oxcarbazepine (OXC)	Oxcarbazepine (OXC) loaded PLGA NPs reduced the number of administrations to 1 over 24 h compared to the free drug thus controlling seizures in rats.	Musumeci et al., 2018
	Thyrotropin-releasing hormone (TRH)	*In vitro* studies showed that the formulation obtained by encapsulating the TRH analogue with PLGA could be an active nanocarrier system.	Kaur et al., 2018

With all this information, it has been observed that the different antiepileptic drugs used are effectively transported to the brain by nano-carrier systems. It is thought that nano-carrier systems may be a new treatment strategy in many CNS disorders, especially in epilepsy.

Conclusion

Epilepsy is a chronic neurological disorder. Many mechanisms underlying the disorder remains a mystery. Besides, the quality of life of the patients is decreasing day by day due to seizures characterized by the disease. Although EEG has been the preferred diagnostic method frequently, the development of imaging methods for the brain is important especially for early diagnosis. Nowadays, there are several treatment options available to reduce the period and frequency of seizures of epilepsy. However, the patient still must struggle with this disease for life. Overall, new approaches are needed in the treatment of other CNS diseases, especially epilepsy. With the recent studies and the development of nanotechnology, it is thought that it is efficient in the treatment of epilepsy compared to classic treatment methods. Designed nanomaterials have perfect advantages owing to their properties such as increasing biocompatibility, increasing blood circulation time, and reducing systemic toxicity, targeting specifically to the region, and

continuous and controlled drug release. However, studies on epilepsy treatment of nano-carrier systems are limited and further studies are needed. Drug delivery systems designed with nanomaterials should be investigated by conducting preclinical studies. We think that it is possible to treat epilepsy with nano-carrier systems.

Conflict of Interest

No conflict of interest is declared by the authors.

References

Alexander, A., Agrawal, M., Uddin, A., Siddique, S., Shehata, A. M., Shaker, M. A., Ata Ur Rahman, S., Abdul, M., & Shaker, M. A. (2019). Recent expansions of novel strategies towards the drug targeting into the brain. *International Journal of Nanomedicine*, *14*, 5895–5909. https://doi.org/10.2147/IJN.S210876

Aronica, E., & Mühlebner, A. (2017). Neuropathology of epilepsy. *Handbook of Clinical Neurology*, *145*, 193–216. https://doi.org/10.1016/B978-0-12-802395-2.00015-8

Beghi E. (2020). The Epidemiology of Epilepsy. *Neuroepidemiology*, *54*(2), 185–191. https://doi.org/10.1159/000503831

Bonferoni, M. C., Rossi, S., Sandri, G., Ferrari, F., Gavini, E., Rassu, G., & Giunchedi, P. (2019). Nanoemulsions for "Nose-to-Brain" Drug Delivery. *Pharmaceutics*, *11*(2), 84. https://doi.org/10.3390/pharmaceutics11020084

Devinsky, O., Vezzani, A., O'Brien, T. J., Jette, N., Scheffer, I. E., de Curtis, M., & Perucca, P. (2018). Epilepsy. *Nature Reviews. Disease Primers*, *4*, 18024. https://doi.org/10.1038/nrdp.2018.24

Ding, C., & Li, Z. (2017). A review of drug release mechanisms from nanocarrier systems. *Materials Science & Engineering. C, Materials For Biological Applications*, *76*, 1440–1453. https://doi.org/10.1016/j.msec.2017.03.130

Erdinç, O. (2013). Principles of therapy in the epilepsies. Nobel Tıp Kitabevleri, İstanbul.

Edwards, C. A., Kouzani, A., Lee, K. H., & Ross, E. K. (2017). Neurostimulation Devices for the Treatment of Neurologic Disorders. *Mayo Clinic Proceedings*, *92*(9), 1427–1444. https://doi.org/10.1016/j.mayocp.2017.05.005

Ergun, E., Salancı, B., Erbas, B. (2017). SPECT and PET in epilepsy, Nuclear Medicine Department, Hacettepe University Faculty of Medicine. *Turkiye Klinikleri J Nucl Med-Special Topics*, 3(2), 123-31.

Fan, X., Chung, J. Y., Lim, Y. X., Li, Z., & Loh, X. J. (2016). Review of Adaptive Programmable Materials and Their Bioapplications. *ACS Applied Materials & Interfaces*, *8*(49), 33351–33370. https://doi.org/10.1021/acsami.6b09110

Feigin, V. L., Nichols, E., Alam, T., Bannick, M. S., Beghi, E., Blake, N., Culpepper, W. J., Dorsey, E. R., Elbaz, A., Ellenbogen, R. G., Fisher, J. L., Fitzmaurice, C., Giussani, G., Glennie, L., James, S. L., Johnson, C. O., et al. (2019). Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*, 18, 459–480.

Fiest, K. M., Sauro, K. M., Wiebe, S., Patten, S. B., Kwon, C. S., Dykeman, J., Pringsheim, T., Lorenzetti, D. L., & Jetté, N. (2017). Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. *Neurology*, *88*(3), 296–303. https://doi.org/10.1212/WNL.0000000000003509

Fisher, R. S., van Emde Boas, W., Blume, W., Elger, C., Genton, P., Lee, P., & Engel, J., Jr (2005). Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia*, *46*(4), 470–472. https://doi.org/10.1111/j.0013-9580.2005.66104.x

Fisher, R. S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J. H., Elger, C. E., Engel, J., Jr, Forsgren, L., French, J. A., Glynn, M., Hesdorffer, D. C., Lee, B. I., Mathern, G. W., Moshé, S. L., Perucca, E., Scheffer, I. E., Tomson, T., Watanabe, M., & Wiebe, S. (2014). ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*, *55*(4), 475–482. https://doi.org/10.1111/epi.12550

Farokhzad, O. C., & Langer, R. (2009). Impact of nanotechnology on drug delivery. *ACS Nano*, *3*(1), 16–20. https://doi.org/10.1021/nn900002m

Huang, R., Zhu, Y., Lin, L., Song, S., Cheng, L., & Zhu, R. (2020). Solid Lipid Nanoparticles Enhanced the Neuroprotective Role of Curcumin against Epilepsy through Activation of Bcl-2 Family and P38 MAPK Pathways. *ACS Chemical Neuroscience*, *11*(13), 1985–1995. https://doi.org/10.1021/acschemneuro.0c00242

Hynes, K., Tarpey, P., Dibbens, L. M., Bayly, M. A., Berkovic, S. F., Smith, R., Raisi, Z. A., Turner, S. J., Brown, N. J., Desai, T. D., Haan, E., Turner, G., Christodoulou, J., Leonard, H., Gill, D., Stratton, M. R., Gecz, J., & Scheffer, I. E. (2010). Epilepsy and mental retardation limited to females with PCDH19 mutations can present de novo or in single generation families. *Journal of Medical Genetics*, *47*(3), 211–216. https://doi.org/10.1136/jmg.2009.068817

Kaur, S., Manhas, P., Swami, A., Bhandari, R., Sharma, K.K., Jain, R., Kumar, R., Pandey, S.K., Kuhad, A., Sharma, R.K., Wangoo, N. (2018). Bioengineered PLGA-chitosan nanoparticles for brain targeted intranasal delivery of antiepileptic TRH analogues. *Chem. Eng. J,* 346, 630–639.

Khan, N., Shah, F. A., Rana, I., Ansari, M. M., Din, F. U., Rizvi, S., Aman, W., Lee, G. Y., Lee, E. S., Kim, J. K., & Zeb, A. (2020). Nanostructured lipid carriers-mediated brain delivery of carbamazepine for improved in vivo anticonvulsant and anxiolytic activity. *International Journal of Pharmaceutics*, *577*, 119033. https://doi.org/10.1016/j.ijpharm.2020.119033

Kınay, D. (2012). Neuroimaging in Epilepsy Surgical Applications. Bakirkoy Prof. Dr. Mazhar Osman Mental and Neurological Diseases Training and Research Hospital 1. Neurology Clinic. *Epilepsi,* 18(1), 18-29. Doi: 10.5505/epilepsi.2012.36035

Kwan, P., Schachter, S. C., & Brodie, M. J. (2011). Drug-resistant epilepsy. *The New England Journal of Medicine*, *365*(10), 919–926. https://doi.org/10.1056/NEJMra1004418

Kwon, C. S., Ripa, V., Al-Awar, O., Panov, F., Ghatan, S., & Jetté, N. (2018). Epilepsy and Neuromodulation-Randomized Controlled Trials. *Brain Sciences*, *8*(4), 69. https://doi.org/10.3390/brainsci8040069

Li, M., Deng, H., Peng, H., & Wang, Q. (2014). Functional nanoparticles in targeting glioma diagnosis and therapies. *Journal of Nanoscience and Nanotechnology*, *14*(1), 415–432. https://doi.org/10.1166/jnn.2014.8757

Liu, M., Du, H., Zhang, W., & Zhai, G. (2017). Internal stimuli-responsive nanocarriers for drug delivery: Design strategies and applications. *Materials Science & Engineering. C, Materials for Biological Applications*, *71*, 1267–1280. https://doi.org/10.1016/j.msec.2016.11.030

Liu, H., Yang, Y., Wang, Y., Tang, H., Zhang, F., Zhang, Y., & Zhao, Y. (2018). Ketogenic diet for treatment of intractable epilepsy in adults: A meta-analysis of observational studies. *Epilepsia Open*, *3*(1), 9–17. https://doi.org/10.1002/epi4.12098

Liu, S., Yang, S., & Ho, P. C. (2018). Intranasal administration of carbamazepine-loaded carboxymethyl chitosan nanoparticles for drug delivery to the brain. *Asian Journal of Pharmaceutical Sciences*, *13*(1), 72–81. https://doi.org/10.1016/j.ajps.2017.09.001

Musumeci, T., Serapide, M. F., Pellitteri, R., Dalpiaz, A., Ferraro, L., Dal Magro, R., Bonaccorso, A., Carbone, C., Veiga, F., Sancini, G., & Puglisi, G. (2018). Oxcarbazepine free or loaded PLGA nanoparticles as effective intranasal approach to control epileptic seizures in rodents. *European Journal of Pharmaceutics and Biopharmaceutics: Official Journal of Arbeitsgemeinschaft Fur Pharmazeutische Verfahrenstechnik e.V*, *133*, 309–320. https://doi.org/10.1016/j.ejpb.2018.11.002

Nour, S. A., Abdelmalak, N. S., Naguib, M. J., Rashed, H. M., & Ibrahim, A. B. (2016). Intranasal brain-targeted clonazepam polymeric micelles for immediate control of status epilepticus: in vitro optimization, ex vivo determination of cytotoxicity, in vivo biodistribution and pharmacodynamics studies. *Drug Delivery*, *23*(9), 3681–3695. https://doi.org/10.1080/10717544.2016.1223216

Nour S. A., Abdelmalak, N. S., Naguib, M. J. (2017). Transferosomes for trans-nasal brain delivery of clonazepam: preparation, optimization, ex-vivo cytotoxicity and pharmacodynamic study. *Journal of Pharmaceutical Research.* 1, 1–15.

Poovaiah, N., Davoudi, Z., Peng, H., Schlichtmann, B., Mallapragada, S., Narasimhan, B. & Wang, Q. (2018). Treatment of neurodegenerative disorders through the blood-brain barrier using nanocarriers. *Nanoscale*, *10*(36), 16962–16983. https://doi.org/10.1039/c8nr04073g

Reif, P. S., Strzelczyk, A., & Rosenow, F. (2016). The history of invasive EEG evaluation in epilepsy patients. *Seizure*, *41*, 191–195. https://doi.org/10.1016/j.seizure.2016.04.006

Ryvlin, P., & Rheims, S. (2008). Epilepsy surgery: eligibility criteria and presurgical evaluation. *Dialogues in Clinical Neuroscience*, *10*(1), 91–103. https://doi.org/10.31887/DCNS.2008.10.1/pryvlinv

Pandolfo M. (2011). Genetics of epilepsy. *Seminars in Neurology*, *31*(5), 506–518. https://doi.org/10.1055/s-0031-1299789

Praveen, A., Aqil, M., Imam, S. S., Ahad, A., Moolakkadath, T., & Ahmad, F. J. (2019). Lamotrigine encapsulated intra-nasal nanoliposome formulation for epilepsy treatment: Formulation design, characterization and nasal toxicity study. *Colloids and Surfaces. B, Biointerfaces*, *174*, 553–562. https://doi.org/10.1016/j.colsurfb.2018.11.025

Rowland, L. P. (2008). Merrit's neurology. Editor; Baslo, B., Gürses, C. Güneş Tıp Kitabevleri. İstanbul. ISBN: 9789752771819.

Samia, O., Hanan, R., & Kamal, e. (2012). Carbamazepine mucoadhesive nanoemulgel (MNEG) as brain targeting delivery system via the olfactory mucosa. *Drug Delivery*, *19*(1), 58–67. https://doi.org/10.3109/10717544.2011.644349

Schmidt, D., & Schachter, S. C. (2014). Drug treatment of epilepsy in adults. *BMJ (Clinical research ed.)*, *348*, g254. https://doi.org/10.1136/bmj.g254

Scioli Montoto, S., Sbaraglini, M. L., Talevi, A., Couyoupetrou, M., Di Ianni, M., Pesce, G. O., Alvarez, V. A., Bruno-Blanch, L. E., Castro, G. R., Ruiz, M. E., & Islan, G. A. (2018). Carbamazepine-loaded solid lipid nanoparticles and nanostructured lipid carriers: Physicochemical characterization and in vitro/in vivo evaluation. *Colloids and Surfaces. B, Biointerfaces*, *167*, 73–81. https://doi.org/10.1016/j.colsurfb.2018.03.052

Scioli Montoto, S., Muraca, G., Di Ianni, M., Couyoupetrou, M., Pesce, G., Islan, G. A., Chain, C.Y., Vela, M.E., Ruiz, M.E., Talevi, A., Castro, G.R. (2021). Preparation, physicochemical and biopharmaceutical characterization of oxcarbazepine-loaded nanostructured lipid carriers as potential antiepileptic devices. *Journal of Drug Delivery Science and Technology*. 63. https://doi.org/10.1016/j.jddst.2021.102470.

Skarpaas, T. L., Jarosiewicz, B., & Morrell, M. J. (2019). Brain-responsive neurostimulation for epilepsy (RNS® System). *Epilepsy Research*, *153*, 68–70. https://doi.org/10.1016/j.eplepsyres.2019.02.003

Téllez-Zenteno, J. F., Hernández-Ronquillo, L., Buckley, S., Zahagun, R., & Rizvi, S. (2014). A validation of the new definition of drug-resistant epilepsy by the International League Against Epilepsy. *Epilepsia*, *55*(6), 829–834. https://doi.org/10.1111/epi.12633

Thurman, D. J., Logroscino, G., Beghi, E., Hauser, W. A., Hesdorffer, D. C., Newton, C. R., Scorza, F. A., Sander, J. W., Tomson, T., & Epidemiology Commission of the International League Against Epilepsy (2017). The burden of premature mortality of epilepsy in high-income countries: A systematic review from the Mortality Task Force of the International League Against Epilepsy. *Epilepsia*, *58*(1), 17–26. https://doi.org/10.1111/epi.13604

Ullah, I., Hussain, M., Qazi, E., Aboalsamh, H. (2018). An automated system for epilepsy detection using EEG brain signals based on deep learning approach. *Expert Systems with Applications,*107(1), 61-71.

Tosi, G., Vilella, A., Chhabra, R., Schmeisser, M. J., Boeckers, T. M., Ruozi, B., Vandelli, M. A., Forni, F., Zoli, M., & Grabrucker, A. M. (2014). Insight on the fate of CNS-targeted nanoparticles. Part II: Intercellular neuronal cell-to-cell transport. *Journal of Controlled Release: Official Journal of The Controlled Release Society*, *177*, 96–107. https://doi.org/10.1016/j.jconrel.2014.01.004

WHO. Epilepsy fact sheet. https://www.who.int/en/news-room/fact-sheets/detail/epilepsy (Accessed 09 December 2020)

Wong, J. C., Shapiro, L., Thelin, J. T., Heaton, E. C., Zaman, R. U., D'Souza, M. J., Murnane, K. S., & Escayg, A. (2021). Nanoparticle encapsulated oxytocin increases resistance to induced seizures and restores social behavior in Scn1a-derived epilepsy. *Neurobiology of Disease*, *147*, 105147. https://doi.org/10.1016/j.nbd.2020.105147

Yalnizoglu, D., Hirfanoglu, T., Serdaroglu, A., Turanli, G., Topcu, M. (2012). Intractable epilepsy in childhood: presurgical evaluation and treatment. Epilepsi: *Journal of The Turkish Epilepsi Society*. 18(1), 7-14.

Yuan, H., & Silberstein, S. D. (2016). Vagus Nerve and Vagus Nerve Stimulation, a Comprehensive Review: Part I. *Headache*, *56*(1), 71–78. https://doi.org/10.1111/head.12647

Yusuf, M., Khan, R. A., Khan, M., & Ahmed, B. (2012). Plausible antioxidant biomechanics and anticonvulsant pharmacological activity of brain-targeted β-carotene nanoparticles. *International Journal of Nanomedicine*, *7*, 4311–4321. https://doi.org/10.2147/IJN.S34588

Zhang, H., Zhai, Y., Wang, J., & Zhai, G. (2016). New progress and prospects: The application of nanogel in drug delivery. *Materials Science & Engineering. C, Materials for Biological Applications*, *60*, 560–568. https://doi.org/10.1016/j.msec.2015.11.041

Zhu, D., Zhang, W. G., Nie, X. D., Ding, S. W., Zhang, D. T., & Yang, L. (2020). Rational design of ultra-small photoluminescent copper nano-dots loaded PLGA micro-vessels for targeted co-delivery of natural piperine molecules for the treatment for epilepsy. *Journal of Photochemistry and Photobiology. B, Biology*, *205*, 111805. https://doi.org/10.1016/j.jphotobiol.2020.111805