

## İlaç Taşıyıcı Sistemlerin Gelişiminde Yapay Zeka Uygulamaları

Gülin AMASYA<sup>1</sup>

### Giriş

Genel olarak ilaç taşıyıcı sistemler, herhangi bir hastalığın tedavisinde kullanılan etken maddeleri yardımcı materyaller ve sistemler aracılığı ile vücuda taşıyan teknolojileri ifade eden geniş bir araştırma alanıdır. Bu teknolojiler; çözelti, tablet, kapsül, merhem, emülsiyon gibi klasik sistemlerden mikro sistemlere ve benzersiz yapısal, kimyasal, mekanik, manyetik, elektriksel ve biyolojik özellikler sergileyen nano ölçekli boyuta sahip yapılara uzanan geniş bir yelpaze sunmaktadır. Ayrıca oral kullanım ya da aşı teknolojileri gibi uygulama yollarını ve tüm vücudu etkileyen etkin maddeleri sistemik olarak vermek yerine, lokal uygulamayı da kapsamaktadır. Kaliteli, etkili ve güvenli bir terapötik etkinlik elde edebilmek için kullanılacak sistem ve yaklaşımların çeşitliliği günümüzde teknolojik ilerlemelerle paralel olarak inanılmaz bir hızla büyümektedir. Bir ilaç molekülünün etkinliği ve güvenliliği onun saf halinden benzersiz bir taşıyıcı sistemine dönüştürerek büyük ölçüde geliştirilebilir ve doğru tasarlanmış bir ilaç taşıyıcı sistem ile biyoyararlanımda artış, yan etki ve toksisitede azalma, hasta uyuncunda artış ya da tamamen yeni tıbbi tedavileri mümkün kılmaya gibi avantajlar elde edilebilir.

<sup>1</sup> Doç. Dr., Ankara Üniversitesi, Eczacılık Fakültesi, Farmasötik Teknoloji AD., gamasya@pharmacy.ankara.edu.tr, 0000-0002-0491-450X

aşamaları etkin maddeye, yardımcı maddelere, ortam ve işlem koşullarına bağlı karmaşık bir süreçtir. Ayrıca nano ilaç taşıyıcı sistemlerin kimyasal bileşimi, yükleme etkinliği, boyut ve dağılımı, şekli, yüzey modifikasyonları gibi fizikokimyasal özelliklerinin tayini için kapsamlı analiz tekniklerinin uygulanması gereklidir. Bu nedenle nano ilaç taşıyıcı sistemlerin çok bileşenli yapısı amaçlanan fizikokimyasal özellikler, biyolojik davranışlar ve farmakolojik profillerle tutarlı bir ürün elde etmek için dikkatli tasarım ve mühendislik gerektirmektedir. Yapay zekâ uygulamalarının karmaşık ve yapılandırılmamış verilerle başa çıkmadaki avantajı göz önünde bulundurulduğunda ilaç taşıyıcı sistemlerin geliştirilmesinde nanoteknolojik uygulamalarla bir arada ele alınması süreci kolaylaştırmak için çok uygundur. Yapay zekâ, makine öğrenimi ve derin öğrenme gibi yaklaşımların nanoteknoloji ile entegrasyonu potansiyel olarak önceden tanımlanmış işlevselliklere sahip yüksek verim ile formüle edilmiş ilaçların rasyonel tasarımını ve gelişimini hızlandırabilir (40, 41).

## Kaynaklar

1. Park H, Otte A, Park K. Evolution of drug delivery systems: From 1950 to 2020 and beyond. *Journal of Controlled Release*. 2022;342:53-65.
2. Yun YH, Lee BK, Park K. Controlled Drug Delivery: Historical perspective for the next generation. *Journal of Controlled Release*. 2015;219:2-7.
3. Hassanzadeh P, Atyabi F, Dinarvand R. The significance of artificial intelligence in drug delivery system design. *Advanced Drug Delivery Reviews*. 2019;151:169-190.
4. Hassani H, Silva ES, Unger S, TajMazinani M, Mac Feely S. Artificial intelligence (AI) or intelligence augmentation (IA): What is the future? *AI*. 2020;1(2):143-155. <https://doi.org/10.3390/ai1020008>
5. Haenlein M, Kaplan A. A brief history of artificial intelligence: On the past, present, and future of artificial intelligence. *California Management Review*. 2019;61(4):5-14.
6. Hamet P, Tremblay J. Artificial intelligence in medicine. *Metabolism*. 2017;69:S36-S40.
7. Vinuesa R, Azizpour H, Leite I, et al. The role of artificial intelligence in achieving the sustainable development goals. *Nature Communications*. 2020;11(1):233. <https://doi.org/10.1038/s41467-019-14108-y>
8. Kersting K. Machine learning and artificial intelligence: two fellow travelers on the quest for intelligent behavior in machines. *Frontiers in Big Data*. 2018;1:Article 6.
9. Nuzzi R, Boscia G, Marolo P, et al. The impact of artificial intelligence and deep learning in eye diseases: A review. *Frontiers in Medicine-Lausanne*. 2021;8:710329. doi: 10.3389/fmed.2021.710329.
10. Sarker IH. Deep learning: a comprehensive overview on techniques, taxonomy, applications and research directions. *SN Computer Science*. 2021;2(6):420. <https://doi.org/10.1007/s42979-021-00815-1>
11. Ekins S. The next era: Deep learning in pharmaceutical research. *Pharmaceutical Research*. 2016; 33(11): 2594-2603. doi:10.1007/s11095-016-2029-7.

12. Zhang L, Tan JJ, Han D, et al. From machine learning to deep learning: progress in machine intelligence for rational drug discovery. *Drug Discovery Today*. 2017;22(11):1680-1685.
13. Alzubaidi L, Zhang JL, Humaidi AJ, et al. Review of deep learning: concepts, CNN architectures, challenges, applications, future directions. *Journal of Big Data*. 2021;8(1):53. <https://doi.org/10.1186/s40537-021-00444-8>
14. Shao F, Shen Z. How can artificial neural networks approximate the brain? *Frontiers in Psychology*. 2023;13. <https://doi.org/10.3389/fpsyg.2022.970214>
15. Patel J, Patel A. Artificial neural networking in controlled drug delivery. Puri M, Pathak Y, Sutariya VK, Tipparaju S, Moreno W (eds.) *Artificial Neural Network for Drug Design, Delivery and Disposition* içinde: Academic Press. 2016:p.195-215. <http://dx.doi.org/10.1016/B978-0-12-801559-9.00010-7>
16. Rafienia M, Amiri M, Janmaleki M, et al. Application of artificial neural networks in controlled drug delivery systems. *Applied Artificial Intelligence*. 2010;24(8):807-820. <http://dx.doi.org/10.1080/08839514.2010.508606>
17. Sutariya VB, Groshev A, Pathak YV. Artificial neural networks in pharmaceutical research, drug delivery and pharmacy curriculum. *Biomedical Engineering Conference (SBEC) Proceeding*. 2013:91-2. <http://dx.doi.org/10.1109/SBEC.2013.54>
18. Montanez-Godinez N, Martinez-Olguin AC, Deeb O, et al. QSAR/QSPR as an application of artificial neural networks. *Methods in Molecular Biology*. 2015;1260:319-333. doi: 10.1007/978-1-4939-2239-0\_19.
19. Baskin II, Winkler D, Tetko IV. A renaissance of neural networks in drug discovery. *Expert Opinion on Drug Discovery*. 2016;11(8):785-795.
20. Zuvela P, David J, Wong MW. Interpretation of ANN-based QSAR models for prediction of antioxidant activity of flavonoids. *Journal of Computational Chemistry*. 2018;39(16):953-963.
21. Marx V. Method of the Year: protein structure prediction. *Nature Methods*. 2022;19(1):5-10. <http://dx.doi.org/10.1038/s41592-021-01359-1>
22. Keyvan K, Sohrabi MR, Motiee F. An intelligent method based on feed-forward artificial neural network and least square support vector machine for the simultaneous spectrophotometric estimation of anti hepatitis C virus drugs in pharmaceutical formulation and biological fluid. *Spectrochimica Acta Part A. Molecular and Biomolecular Spectroscopy*. 2021;263: 120190.
23. Ayres LB, Gomez FJV, Linton JR, et al. Taking the leap between analytical chemistry and artificial intelligence: A tutorial review. *Analytical Chimica Acta*. 2021;1161.
24. Jariwala N, Putta CL, Gatade K, et al. Intriguing of pharmaceutical product development processes with the help of artificial intelligence and deep/machine learning or artificial neural network. *Journal of Drug Delivery Science and Technology*. 2023;87.
25. Ma CW, Ren Y, Yang JR, et al. Improved peptide retention time prediction in liquid chromatography through deep learning. *Analytical Chemistry*. 2018;90(18):10881-10888.
26. Melnikov AD, Tsentalovich YP, Yanshole VV. Deep learning for the precise peak detection in high-resolution LC-MS data. *Analytical Chemistry*. 2020;92(1):588-592.
27. ICH guideline Q8 (R2) on pharmaceutical development [Internet]. 2017.
28. Amasya G, Şengel-Türk, CT. Formülasyon tasarımı ve dozaj formu geliştirilmesi. Alp M (ed.) *İlaç Keşfi ve Geliştirilmesi* içinde: Akademisyen Yayınevi; 2021. p. 107-131.
29. Khalid GM, Usman AG. Application of data-intelligence algorithms for modeling the compaction performance of new pharmaceutical excipients. *Future Journal of Pharmaceutical Sciences*. 2021;7(1):31.
30. Damiati SA, Martini LG, Smith NW, et al. Application of machine learning in prediction of hydrotrope-enhanced solubilisation of indomethacin. *International Journal of Pharmaceu-*

- tics*. 2017;530(1-2):99-106.
31. Onuki Y, Kawai S, Arai H, et al. Contribution of the physicochemical properties of active pharmaceutical ingredients to tablet properties identified by ensemble artificial neural networks and kohonen's self-organizing maps. *Journal of Pharmaceutical Sciences*. 2012;101(7):2372-2381.
  32. Ebube NK, Owusu-Ababio G, Adeyeye CM. Preformulation studies and characterization of the physicochemical properties of amorphous polymers using artificial neural networks. *International Journal of Pharmaceutics*. 2000;196(1):27-35.
  33. Rojek B, Suchacz B, Wesolowski M. Artificial neural networks as a supporting tool for compatibility study based on thermogravimetric data. *Thermochima Acta*. 2018;659:222-231.
  34. Ibric S, Jovanovic M, Djuric Z, et al. Generalized regression neural networks in prediction of drug stability. *Journal of Pharmacy and Pharmacology*. 2007;59(5):745-750.
  35. Han R, Yang YL, Li XS, et al. Predicting oral disintegrating tablet formulations by neural network techniques. *Asian Journal of Pharmaceutical Sciences*. 2018;13(4):336-342.
  36. Takagaki K, Arai H, Takayama K. Creation of a tablet database containing several active ingredients and prediction of their pharmaceutical characteristics based on ensemble artificial neural networks. *Journal of Pharmaceutical Sciences*. 2010;99(10):4201-4214.
  37. Lefnaoui S, Rebouh S, Bouhedda M, et al. Artificial neural network for modeling formulation and drug permeation of topical patches containing diclofenac sodium. *Drug Delivery and Translational Research*. 2020;10(1):168-184.
  38. Manda A, Walker RB, Khamanga SMM. An artificial neural network approach to predict the effects of formulation and process variables on prednisone release from a multipartite system. *Pharmaceutics*. 2019;11(3).
  39. Khan AM, Hanif M, Bukhari NI, et al. Artificial neural network (ANN) approach to predict an optimized pH-dependent mesalamine matrix tablet. *Drug Design Development and Therapy*. 2020;14:2435-2448.
  40. Serov N, Vinogradov V. Artificial intelligence to bring nanomedicine to life. *Advanced Drug Delivery Reviews*. 2022;184.
  41. Alshawwa SZ, Kassem AA, Farid RM, et al. Nanocarrier drug delivery systems: characterization, limitations, future perspectives and implementation of artificial intelligence. *Pharmaceutics*. 2022;14(4).
  42. Dawoud MH, Mannaa IS, Abdel-Daim A, et al. Integrating artificial intelligence with quality by design in the formulation of lecithin/chitosan nanoparticles of a poorly water-soluble drug. *AAPS PharmSciTech*. 2023;24(6).
  43. El Menshawe SF, Aboud HM, Elkomy MH, et al. A novel nanogel loaded with chitosan decorated bilosomes for transdermal delivery of terbutaline sulfate: artificial neural network optimization, in vitro characterization and in vivo evaluation. *Drug Delivery and Translational Research*. 2020;10(2):471-485. doi: 10.1007/s13346-019-00688-1.
  44. Maharjan R, Hada S, Lee JE, et al. Comparative study of lipid nanoparticle-based mRNA vaccine bioprocess with machine learning and combinatorial artificial neural network-design of experiment approach. *International Journal of Pharmaceutics*. 2023;640.
  45. Haider T, Soni V. Response surface methodology and artificial neural network-based modeling and optimization of phosphatidylserine targeted nanocarriers for effective treatment of cancer: In vitro and in silico studies. *Journal of Drug Delivery Science and Technology*. 2022;75.
  46. Esmaeili F, Aghajani M, Rashti A, et al. Parameters influencing size of electrosprayed chitosan/HPMC/TPP nanoparticles containing alendronate by an artificial neural networks model. *Journal of Electrostatics*. 2021;112.
  47. Han R, Ye ZYF, Zhang YS, et al. Predicting liposome formulations by the integrated machi-

- ne learning and molecular modeling approaches. *Asian Journal of Pharmaceutical Sciences*. 2023;18(3):100811.
48. Elkomy MH, Elmenshawe SF, Eid HM, et al. Topical ketoprofen nanogel: artificial neural network optimization, clustered bootstrap validation, and in vivo activity evaluation based on longitudinal dose response modeling. *Drug Delivery*. 2016;23(9):3294-3306.
  49. Youshia J, Ali ME, Lamprecht A. Artificial neural network based particle size prediction of polymeric nanoparticles. *European Journal of Pharmaceutics and Biopharmaceutics*. 2017;119:333-342.
  50. He Y, Ye ZYF, Liu XY, et al. Can machine learning predict drug nanocrystals? *Journal of Controlled Release*. 2020;322:274-285.
  51. Bozuyuk U, Dogan NO, Kizilel S. Deep insight into PEGylation of bioadhesive chitosan nanoparticles: Sensitivity study for the key parameters through artificial neural network model. *ACS Applied Materials & Interfaces*. 2018;10(40):33945-33955.
  52. Maleki H, Naghibzadeh M, Amani A, et al. Preparation of paclitaxel and etoposide co-loaded mPEG-PLGA nanoparticles: an investigation with artificial neural network. *Journal of Pharmaceutical Innovation*. 2021;16(1):11-25. <http://dx.doi.org/10.1007/s12247-019-09419-y>
  53. Rebollo R, Oyoum F, Corvis Y, et al. Microfluidic manufacturing of liposomes: development and optimization by design of experiment and machine learning. *ACS Applied Materials & Interfaces*. 2022; 14(35):39736-39745. doi: 10.1021/acsami.2c06627.
  54. Amasya G, Aksu B, Badilli U, et al. QbD guided early pharmaceutical development study: Production of lipid nanoparticles by high pressure homogenization for skin cancer treatment. *International Journal of Pharmaceutics*. 2019;563:110-121.