Cryochemical Formation of Drug Nanoforms: Approach to Directed Drug Delivery and Controlled Drug Release

Tatyana I. Shabatina[1,2*], Yu.N.Morosov[1,2], Irina V. Astashova[3], Mikhail Ya.Melnikov[1]
[1] Lomonosov Moscow State University, Department of Chemistry, Leninskie Gori build. 1/3 119991 Moscow, Russia
[2]Bauman Moscow Technical State University, Faculty of Fundamental Sciences, 2-nd Bauman Street, build.5, Moscow 105005, Russia
[3]Lomonosov Moscow State University, Department of Mechanic and Mathematics; Moscow, 119991, Russia

The use of medicinal substances in nanosized forms (nanoforms, nanoparticles) allows pharmaceutical preparations to increase their therapeutic effectiveness due to several factors: high specific surface area of nanomaterials; high concentration of surface-active centers interacting with biological objects. In the case of drug nanoforms even low concentrations of a bioactive substance can have a significant therapeutic effect on living organisms. These facts lead pharmacists to use lower doses of active components and in consequence to lower side toxic effects of pharmaceutical preparations in nanoforms. It is known for many drug substances, which are commonly used nowadays, to be poorly soluble in water, so they have insufficient bioavailability. Converting them into nanoforms will increase the rate of dissolution and increased saturation solubility of drug nanocrystals rising their bioavailability, and thus makes a significant contribution to their higher therapeutic efficiency. Some physical and chemical methods can contribute to the formation of both pure drug nanoparticles and their ligand or polymer-covered nanoforms, which are characterized by higher stability.

Cryochemical modification is a powerful method of reducing the size of drug substances particles, changing their form and crystal structure in order to transfer them in nanoforms and improve their pharmaceutical properties. An application of this method allowed us to obtain antibiotics nanocrystals and their hybrid nanocomposites with metal particles. Antibacterial compositions were produced by low temperature drug and metal vapors co-deposition or cryogenic freeze drying technique of mixed water solutions containing silver or copper nanoparticles and antibacterial components dioxidine or gentamicin [1, 2]. The thorough investigations TEM, electron microdiffraction, Fourier transformation infrared spectroscopy (FTIR), UV absorption spectroscopy, X-ray diffraction, differential thermal analysis (DTA) were made, It was shown that the hybrid compositions were including Ag and/or Cu nanoparticles of 5-70 nm in diameter and nanoparticles of antibiotics of 50-250 nm in diameter. Drug cryochemical forms possessed modified crystal structures and lower melting temperatures, New cryoformed hybrid composites of nanosized metal and antibiotic particles demonstrates higher antibacterial activity against *E. coli 52, S.aureus 144, M. cyaneum 98, B. cereus 9* compared to the original drug substance and individual metal nanoparticles.

The comprehensive mathematic models describing the different stages of cryomodification processes developed will give us the base for finding of the optimal values of different physico-chemical parameters for producing of drug nanoforms with desired therapeutic effects and bioavailability.

Acknowledgements. The work is financially supported by the State Scientific Program of the MSU Development, MSU Interdisciplinary Grants for Scientific Schools, NSH – 2023-05-0026.

1. Shabatina, T.I.; Morosov, Y.N.; Soloviev, A.V.; Shabatin, A.V.; Vernaya, O.I.; Melnikov, M.Y. Cryochemical Production of Drug Nanoforms: Particle Size and Crystal Phase Control of the Antibacterial Medication 2,3-Quinoxalinedimethanol-1,4-dioxide (Dioxidine). *Nanomaterials* **2021**, *11*, 1588. https://doi.org/10.3390/nano11061588
2. Shabatina, T.I.; Vernaya, O.I.; Melnikov, M.Y. Hybrid Nanosystems of Antibiotics with Metal Nanoparticles - Novel Antibacterial Agents. *Molecules* **2023**, *28*, 1603. https://doi.org/10.3390/molecules28041603