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BIOACTIVE GLASS IN NEUROTECHNOLOGIES: TECHNOLOGICAL AND ENGINEERING ASPECTS OF DEVELOPMENT

Assoc. Prof. Olena Khomenko, PhD
Department of Chemical Technology of Ceramics, Glass and Building Materials
Ukrainian State University of Science and Technology, Ukraine
E-mail: o.s.khomenko@ust.edu.ua

Prof. Tsvetan Dimitrov, PhD
Branch Razgrad
University of Ruse "Angel Kanchev", Bulgaria
E-mail: tz_dimitrow@abv.bg

Stud. Valeria Larchikova
Department of Chemical Technology of Ceramics, Glass and Building Materials
Ukrainian State University of Science and Technology, Ukraine
E-mail: elenahtks@ukr.net

Assoc. Prof. Sergey Rokutov, PhD (Medicine)
Department of Physical Therapy, Occupational Therapy
Ukrainian State University of Science and Technology, Ukraine
E-mail: rokutov@ukr.net

Abstract: *Modern trends in neurotechnology are focused on developing materials that can not only replace damaged regions of nervous tissue but also actively stimulate neurogenesis, angiogenesis, and neural integration. The aim of this study was to analyze the technological features of the synthesis and modification of bioactive glass suitable for application in neurotechnological systems, and to identify promising directions for integrating bioglass into the design of neural implants and regenerative platforms. The results obtained indicate that the incorporation of electroactive ions (Na^+, Li^+, Cu^{2+}) into the structure of bioactive glass enhances its electrical conductivity and enables its use in neural implants and biosensors that interact with cells through electrochemical signaling. Sol–gel technology enables the fabrication of nanoporous glass matrices with high surface activity, suitable for the immobilization of neurotrophic factors (NGF, BDNF), which promote neuronal growth in vitro. The integration of bioactive glass into neuroengineering devices allows the combination of regenerative, electrochemical, and sensory functions, paving the way for the development of "smart" biointerfaces for future medicine. Further research should focus on assessing the in vivo biocompatibility of such systems and optimizing their integration with neural tissue.*

Keywords: *Bioactive Glass, Neurotechnology, Sol-Gel Synthesis, 3d Printing, Neuroengineering, Implants, Nanostructures*

INTRODUCTION

Neurotechnologies combine neuroscience, engineering, biotechnology, informatics, and medicine to create technologies that enable the study, restoration, modification, or interaction with the nervous system (Vitale, F., Gelinas, J. N., Cabrera, L. Y., 2022). Today, this interdisciplinary field requires materials that are not merely inert "scaffolds" but actively stimulate the regeneration of neural tissue—neurogenesis, angiogenesis, and functional integration of implants with neurocytes. Among such materials is bioactive glass (Kargozar, S., Mozafari, M., Ghenaatgar-Kasbi, M., Baino, F., 2020), distinguished by its ability to form a bioactive apatite layer, controlled ion release, and chemical modifiability. In the future, this material may find applications in neural implants, conductive guides for electrical stimulation, and regenerative platforms.

Two main approaches to producing bioactive glasses are traditional melt-quenching and sol–gel processing.

The production of bioactive glasses by the melting method involves mixing oxide components and heating them to high temperatures (1300–1500 °C), where they form a homogeneous melt that is rapidly cooled to create a glassy matrix (Ben-Arfa, B.A.E., Pullar, R.C., 2020; Хоменко О.С., Амеліна О.С., Зайчук О.В., Прохоренко І.О., Сігунов О.О., Македонська-Білих О.М., Шейкус А.Р., 2025). The advantages of this method include high mechanical strength of the product, good compositional reproducibility, and ease of scaling for industrial production. The main drawbacks are limited porosity, lower surface reactivity (compared to sol–gel materials), and difficulty in incorporating thermosensitive modifying components due to the high processing temperatures.

The sol–gel method provides higher specific surface area, porosity, and biological reactivity, as well as facilitates the incorporation of modifying additives (metal ions, pharmacological agents) and the formation of mesoporous structures, which are important for controlled ion release and cell colonization (Fiume, E, Migneco, C, Verné, E, Baino F., 2020). However, the disadvantages of this method include high sensitivity to technological process factors (solution temperature, component concentration, mixing speed, etc.) and challenges in scaling.

The shaping methods for implantable materials from bioactive glasses are quite diverse and include 3D printing, electrospinning, thermopressing, and combined composite approaches (Rajzer, I., Kurowska, A., Frankova, J., Sklenářová, R., Nikodem, A., Dziadek, M., Jabłoński, A., Janusz, J., Szczygieł, P., Ziąbka, M., 2023). These methods allow the production of porous scaffolds, fibers, and coatings compatible with soft-tissue neural interfaces. Combining bioactive glasses with elastic polymer matrices (hydrogels, elastomers) helps reduce the mechanical mismatch between the implant and brain/nerve tissue (Słota, D., Niziołek, K., Kosińska, E., Sadlik, J., Sobczak-Kupiec, A., 2025).

Bioactive glass can be applied in neurotechnologies primarily due to its ionic solubility: upon contact with body fluids, the glass releases bioactive ions (e.g., Si, Ca, Na), which can stimulate neuron survival, neurite outgrowth (neuritogenesis), and angiogenesis (Kargozar, S., Mozafari, M., Ghenaatgar-Kasbi, M., Baino, F., 2020). Boron-based bioactive glass supports (Marquardt, L.M., Day, D., Sakiyama-Elbert, S. E., Harkins, A. B., 2014) neuronal viability and stimulates neurite extension in embryonic ganglion cultures. Furthermore, thanks to the ability to combine bioglass with polymer matrices (e.g., 3D scaffolds or fibers), biocomposites can be created that provide not only a biocompatible environment but also the mechanical and structural properties needed for guided nerve tissue regeneration.

The most interesting ions in terms of influencing neurogenesis in bioactive glasses are Na^+, Li^+, and Cu^{2+}. Sodium-containing components of traditional bioactive glasses provide significant ionic conductivity due to the mobility of Na^+ in the glass matrix. This is useful for creating materials with moderate ionic conductivity that can participate in electrochemical interactions with neurons. Conduction in phosphosilicate systems is often controlled by “hopping” of sodium ions, which allows tuning conductivity parameters by changing Na_2O concentration (Wójcik, N. A., Jonson, B., Barczyński, R. J., Kupracz, P., Möncke, D., Ali, S., 2018).

The addition of lithium to the glass composition has recently attracted attention due to the neuroprotective and neurogenic effects of Li ions (impact on GSK-3β, Wnt signaling pathways), as well as changes in glass tectonics that can affect degradation and ion release (Farmani, A. R., Salmeh, M. A., Golkar, Z., Moeinzadeh, A., Ghiasi, F. F., 2022). Li-doped bioactive glasses demonstrate pronounced biological activity in regeneration models and promote healing with neuro-support; at the same time, Li^+ addition alters glass structure and glass transition temperature, which is technically important during synthesis.

The incorporation of copper ions into bioactive glasses can induce pro-angiogenic effects and stimulate cell migration/proliferation; Cu ions in mesoporous bioactive glasses can promote angiogenesis and improve implant integration into tissue, which is crucial for nerve regeneration (Romero-Sánchez, L. B., Marí-Beffa, M., Carrillo, P., Medina, M. Á., Díaz-Cuenca, A., 2018).

Collective evidence suggests that combined introduction of electroactive ions (Na^+ as the basis for ionic conductivity, Li^+ for neuroprotection/stimulation, Cu^{2+} for angiogenesis) enables the synthesis of bioactive glasses with improved electrochemical interaction with neurons, paving the way for use in electrically interactive implants and biosensors. However, the biological effect depends on dosage and ion release kinetics (Wójcik, N. A., Jonson, B., Barczyński, R. J., Kupracz, P., Möncke, D., Ali, S., 2018).

Due to the complexity and diversity of tasks in creating neuroprotective materials, many challenges remain. Strict control of degradation and ion release rate is required. Excessive or rapid release of Cu^{2+} or Li^{+} can be cytotoxic; clear release profiles and in vivo models are needed (Romero-Sánchez, L. B., Marí-Beffa, M., Carrillo, P., Medina, M. Á., Díaz-Cuenca, A., 2018). Glass is a stiffer material, so compositions with polymers must be developed for implants in soft neural tissues to avoid micromovements and chronic inflammation (Yang, S., Qiao, X., Ma, J., Yang, Z., Luo, X., Du, Z., 2025). Ensuring low impedance, stable electrode signals, and minimal artifacts while maintaining bioactivity is a technical challenge requiring multifactor optimization (Wang, J., Fang, J., Weng, Z., Nan, L., Chen, Y., 2025). Reproducibility of sol–gel processes, sterility, and biocompatibility standards are key barriers to clinical translation (Fiume, E., Migneco, C., Verné, E., Baino F., 2020).

EXPOSITION

The aim of this study was to investigate the effect of adding sodium, lithium, and copper oxides in an amount of 2 wt. % on the dissolution rate of bioactive glasses based on the traditional 45S5 composition in a physiological medium. The base composition of the bioactive glass, wt.%: 45.0 SiO_2, 24.5 CaO, 24.5 Na_2O, 6 P_2O_5. The physiological medium used was Ringer's solution. To introduce the oxides, the following reagents were used: marshite, sodium and calcium carbonates, ammonium dihydrogen phosphate, as well as chemically pure salts of lithium nitrate and copper carbonate. The glasses were melted at 1350 °C in corundum crucibles, and the melt was quenched by pouring into distilled water.

The method for determining the solubility of bioactive glasses in this study involved isolating a fraction of glass particles sized 0.5–1.0 mm to ensure equal surface area for all samples. For this purpose, the bioactive glass was ground in a mortar and sieved through appropriate meshes. The samples were weighed using Radwag AS 220.R2 analytical balances (accuracy 0.0001 g) and immersed in Ringer's solution at a ratio of 1 g per 50 mL of solution. The containers with the physiological solution were kept in an incubator at 37 °C for 7 days. After this period, the glass samples were filtered, rinsed with distilled water, the ash-free filter was calcined at 400 °C, and the glass samples were weighed. The mass loss was used to determine the solubility of the tested glasses.

Figure 1 shows the results of determining the solubility index of bioactive glasses depending on the added metallic ions

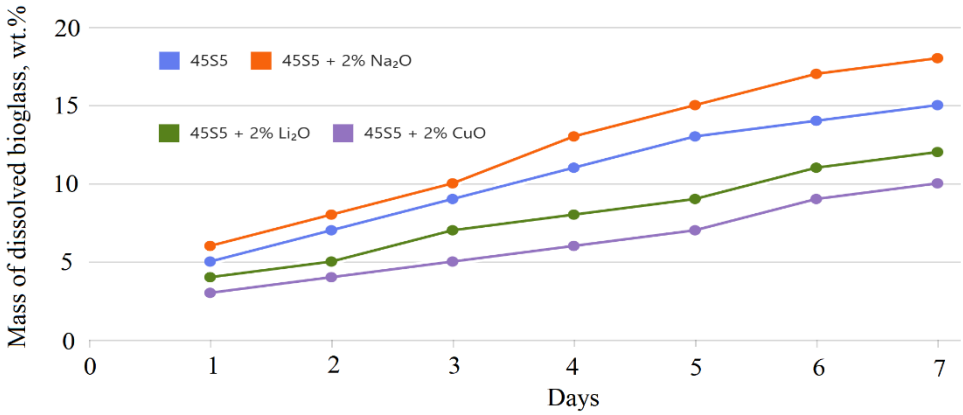

Fig. 1 Dependence of bioactive glass solubility on the added metallic ions

From the figure, it is evident that the mass loss of the base 45S5 bioactive glass over 7 days increases from 5 to 15 wt.%. Increasing the Na_2O content in the glass by 2 wt.% leads to higher solubility—the value reaches 18 wt.%, indicating enhanced ionic mobility. The addition of Li_2O reduces the dissolution rate (to about 12 %), likely due to structural stabilization. Dissolution is slowed even further by adding CuO—down to about 10 %, which may be associated with the formation of a denser hydroxyapatite layer during ion exchange (Хоменко О. С., Амеліна О. А., Зайчук О. В., Прохоренко І. О., Сігунов О. О., Македонська-Білих О. М., Шейкус А. Р., 2025).

The ion-exchange mechanism between bioactive glass and physiological solution is complex and multi-stage. In the initial period, ion exchange $Na^{+} \leftrightarrow H^{+}/H_3O^{+}$ occurs, forming silanol groups (Si–OH). Next, hydrolysis of Si–O–Si bonds takes place, leading to the formation of a porous layer. This is followed by the release of Ca^{2+} and PO_4^{3-} ions and subsequent apatite nucleation.

The addition of Na_2O accelerates dissolution (up to 18 %) because it increases the number of network modifiers, reducing the degree of silicate network polymerization and enhancing ionic mobility. Li_2O decreases the degradation rate (to about 12 %) due to the formation of a more stable structure, as lithium has a smaller ionic radius and increases network density. CuO results in the lowest solubility (around 10 %), likely due to the formation of a protective corrosion product layer and possible involvement of Cu^{2+} in forming a denser surface phase.

Thus, dissolution is controlled by ion diffusion and silicate network hydrolysis. Composition changes affect Si–O bond energy and the rate of hydroxyapatite formation, which determines degradation kinetics.

The slowdown in dissolution is clearly illustrated in Figure 2, which shows the dissolution rate (gradient) and visually represents the described mechanisms.

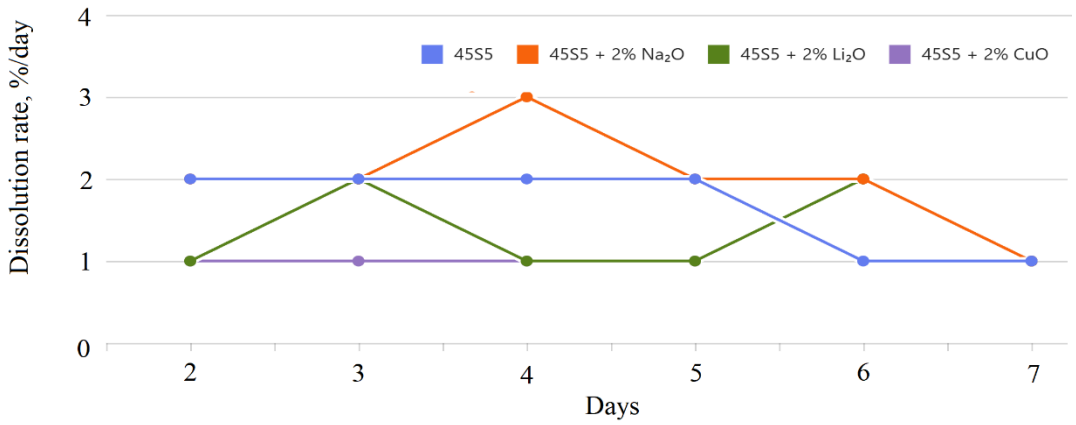

Fig. 2 Dissolution rate (gradient) of the studied bioactive glasses

For the base 45S5 glass, a stable increase in dissolution rate is observed at the beginning (≈2% per day), followed by a gradual decrease, which may be associated with the formation of hydroxyapatite - the mineral analog of bone (Хоменко О. С., Амеліна О. А., Зайчук О. В., Прохоренко І. О., Сігунов О. О., Македонська-Білих О. М., Шейкус А. Р., 2025). When Na_2O is added, the highest peak rates are observed (up to 3 % per day), confirming active ionic diffusion. The addition of Li_2O clearly demonstrates lower dissolution rates (1–2 % per day) and a stabilizing effect, while the introduction of CuO results in the lowest dissolution rate of the glass (≈1 % per day).

Considering the potential toxic effect of lithium and copper ions, further calculations were made based on the determined dissolution rates to estimate the amount of oxides that could enter the human body when an implant made of bioactive glass weighing 5 g is implanted:

-Release of Cu^{2+} ions (from 45S5 + 2 % CuO):

Mass of Cu per day: ≈0.0008 g (at 1 % per day), up to 0.0016 g (at 2 % per day).

Moles of Cu: $\approx 1.3\times10^{-5}$ mol/day.

Number of atoms: $\approx 7.6\times10^{18}$ atoms/day (doubles at 2% per day).

-Release of Li^{+} ions (from 45S5 + 2 % Li_2O):

Mass of Li per day: ≈0.00047 g (at 1 % per day), up to 0.00093 g (at 2 % per day).

Moles of Li: $\approx 6.7\times10^{-5}$ mol/day.

Number of atoms: $\approx 4.0\times10^{19}$ atoms/day (doubles at 2 % per day).

From these calculations, it is evident that lithium is released in an amount approximately five times greater than copper, due to its lower molar mass and higher proportion of the element in the oxide. Such concentrations may be significant for biological effects: Li^{+} stimulates osteogenesis, while Cu^{2+} has angiogenic and antibacterial effects, but requires careful control to avoid toxicity.

Copper is an essential trace element, but its excess is toxic. According to WHO and sanitary standards, the maximum permissible concentration of copper in drinking water is 2 mg/L. Exceeding this level can lead to gastrointestinal disorders, and chronic excess may cause liver and kidney damage (World Health Organization, 2022). The daily dietary requirement for adults is about 0.9 mg/day, while toxic effects are observed with intake exceeding 10 mg/day over a prolonged period (National Academies of

Sciences, Engineering, and Medicine, 2001). The mechanism of toxicity: Cu^{2+} ions bind to proteins (especially enzymes), disrupting their structure and function, which can cause oxidative stress (Crawley, L., Chakrabarti, S., Oteiza, P. I., 2004).

Lithium is not an essential element but is used in pharmacology (lithium salts for the treatment of bipolar disorder). The therapeutic concentration of lithium in blood plasma is 0.6–1.2 mmol/L. Toxicity begins at levels >1.5 mmol/L, and >2.5 mmol/L is considered life-threatening (possible nervous system disorders, cardiac arrhythmias, renal failure). Lithium has a narrow therapeutic range, so even a slight excess can be critical (Gitlin, M., 2016).

Table 1 presents comparative data for the studied ions regarding their effects on the human body.

Table 1 Comparison of safe and toxic levels of Cu^{2+} and Li^{+} ions

Parameter	Cu^{2+} (Copper)	Li^{+} (Lithium)
Physiological role	Essential trace element (enzymes, angiogenesis)	Not essential, pharmacological use
Daily requirement	≈ 0.9 mg/day	Not established (therapeutic administration)
WHO limit in drinking water	2 mg/L	No standard (not a natural component)
Therapeutic range in plasma	0.6–1.2 mmol/L	>10 mg/day (chronic)
Toxic threshold	>1.5 mmol/L (onset of toxicity)	>30 mg/day (acute intoxication)
Dangerous level	>2.5 mmol/L (life-threatening risk)|	>30 mg/day (acute intoxication)
Main toxic effects	Gastrointestinal disorders, liver and kidney damage, oxidative stress	Neurological disorders, arrhythmias, renal failure

Analysis in the context of a 5 g implant:

Based on the obtained calculations, Cu^{2+} is released at approximately 0.0008–0.0016 g/day (0.8–1.6 mg), which is below the toxic threshold and close to the daily requirement; Li^{+} is released at approximately 0.00047–0.00093 g/day (0.47–0.93 mg), which, when converted to concentration in a local environment (e.g., 50 mL), gives about 0.19–0.37 mmol/L—below the therapeutic threshold but sufficient for a local biological effect.

CONCLUSION

Thus, bioactive glasses as a basis for creating restorative neural systems can be applied in various forms. Thin layers of bioactive glass on metallic electrodes improve biocompatibility, reduce immune response, and can enhance electrochemical contact due to increased ionic conductivity. Bioactive glass as porous scaffolds combined with hydrogel composites can serve as carriers for guided axonal growth and controlled release of growth factors. Functional 3D-printed glass-based implants allow precise tuning of dopant distribution and mechanical properties for specific neural regions.

Promising directions for future research include the development of multimodal composites (bioactive glass and conductive polymer/carbon nanostructures) for combined electrical stimulation and ion therapy, mechanisms for precise dosing of ionic “packets” in mesopores for controlled, localized effects on neurons and blood vessels, integration with soft electronic interfaces and sensors for closed-loop feedback in neuroprosthetics, and more.

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