

# Diffusion-Controlled Crystallization Inspired by Biomineralization, and Its Bioapplications

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Crystallization in nature occurs under diffusion-limited conditions, contrasting with conventional studies in solution or gaseous phases where diffusion is unrestricted. Hydrogels, which significantly slow down ion transport, provide a biomimetic environment for studying crystallization mechanisms. The controlled diffusion within hydrogels affects crystallization at multiple scales: it localizes crystal growth macroscopically,<sup>[1-3]</sup> interacts with organic fibers microscopically,<sup>[4,5]</sup> and chemically modulates phase selection at the molecular level.<sup>[6-9]</sup> By leveraging hydrogel-mediated crystallization, insights into biomineralization and material synthesis have been gained across different mineral systems.

Using an orthogonal diffusion method, calcium carbonate crystallization was spatially controlled within a single hydrogel. Precise regulation of hydrogen carbonate and hydroxide ion diffusion enabled phase selection between calcite and vaterite by modulating local pH and supersaturation. Unlike rapid precipitation in solution-based methods, hydrogel-mediated slow diffusion stabilized transient phases and intermediates, offering a platform to study phase transitions in biomineralization. Notably, vaterite, a metastable phase rarely observed in biological settings, was stabilized within the hydrogel matrix, suggesting potential applications in drug delivery and biomaterial coatings due to its high surface area and biodegradability.

Similarly, calcium phosphate phases—dicalcium phosphate dihydrate, hydroxyapatite, and amorphous calcium phosphate—were synthesized within a hydrogel-based dual diffusion system by controlling calcium and hydroxide ion fluxes. This system produced distinct mineral phases in response to local pH changes, forming plate-like dicalcium phosphate dihydrate, sea urchin-shaped hydroxyapatite, and spherical amorphous calcium phosphate. When bone-derived mesenchymal stem cells were cultured on these phases, differential gene expression of RUNX2 and OPN was observed. This study demonstrates the potential of hydrogel systems for biomimetic mineralization and bone tissue engineering, highlighting their role in directing phase-specific crystallization and cellular responses.

[1] Jo, M. K., Cho, Y. S., Holló, G., Choi, J. M., Lagzi, I. & Yang, S. H. (2021). *Cryst. Growth. Des.*, **21**, 6199.

[2] Cho, Y. S., Moon, M., Holló, G., Lagzi, I. & Yang, S. H. (2022). *Langmuir*, **38**, 2515.

[3] Kim, H., Holló, G., Heo, C. M., Lagzi, I., Lee, H. & Yang, S. H. (2024). *Cryst. Growth. Des.*, **24**, 8794-8802.

[4] Jo, M. K., Oh, Y., Kim, H. J., Kim, H. L. & Yang, S. H. (2020). *Cryst. Growth. Des.*, **20**, 560.

[5] Kim, H. L., Shin, Y. S. & Yang, S. H. (2022). *CrystEngComm*, **24**, 1344.

[6] Jung, J. & Yang, S. H. (2023). *Cryst. Growth. Des.*, **23**, 8753-8760.

[7] Shin, Y. S., Jo, M. K., Cho, Y. S. & Yang, S. H. (2021). *ACS Omega*, **7**, 1173.

[8] Shin, Y. S., Holló, G., Lagzi, I. & Yang, S. H. (2024). *Cryst. Growth. Des.*, **24**, 9994-10002.

[9] Cho, Y. S.; Heo, C. M.; Gebauer, D.; Yang, S. H. (2025). *Cryst. Growth. Des.*, **25**, 2960-2969