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Editorial

Supramolecular assembly nanoparticle for trans-epithelial treatment of keratoconus

Keratoconus is a clinically prevalent corneal ectasia, characterized by progressive thinning and conical protrusion of the central cornea [1]. With an incidence rate of one in every 400 to 2000 individuals, it stands as a leading cause of blindness among the youth. To date, there are no pharmacological interventions available for the treatment of keratoconus. In advanced cases culminating in blindness, corneal transplantation remains the only restorative option. However, this surgical procedure carries risks of immune rejection and chronic graft failure.

Riboflavin (RF)-corneal collagen crosslinking (CXL) represents the sole alternative to corneal transplant; yet, this technique is not without drawbacks [2]. Hydrophilic nature of riboflavin molecules results in low corneal permeation, often necessitating the painful and complication-prone removal of the corneal epithelium. Additionally, reliance on ultraviolet light exposure during the procedure can lead to irreversible damage to corneal cells and a host of post-operative complications. Consequently, the development of a highly permeable crosslinking agent capable of trans-epithelial delivery is of paramount importance [3]. Such an advancement would mark a significant shift in keratoconus treatment, moving from surgical intervention to a non-invasive pharmacotherapeutic approach. Achieving this would represent a substantial stride forward in the clinical management of keratoconus.

The emergence of nanotechnology has provided new opportunities for developing trans-epithelial drug delivery strategies, which require efficient permeation through the corneal stroma [4]. Supramolecular assembly technology has demonstrated its unique advantages in the construction of nanoparticles, especially in terms of controlling their size, surface interface properties, and morphology, offering unparalleled control capabilities in transmembrane drug delivery. These nanotechnological advancements offer promising avenues to enhance ocular drug delivery, potentially overcoming the limitations posed by the eye's protective barriers.

Professors Xingtao Zhou, Jinhai Huang, Rongrong Gao and colleagues from Fudan University published a study in *Advanced Materials* introducing a novel nanomaterial [5]. They developed a microsphere composite (RF@ZIF-8 NF) that resembles hibiscus flowers in structure based on the supramolecular assembly of riboflavin and zeolitic imidazolate (Fig. 1). This innovative material was designed to enhance the permeability of the corneal epithelium, facilitating CXL therapy aimed at slowing or halting the progression of keratoconus.

Researchers ingeniously disrupted the self-assembly of ZIF-8 using riboflavin and successfully re-established the intermolecular mechanisms among riboflavin, 2-methylimidazole (2-mim),

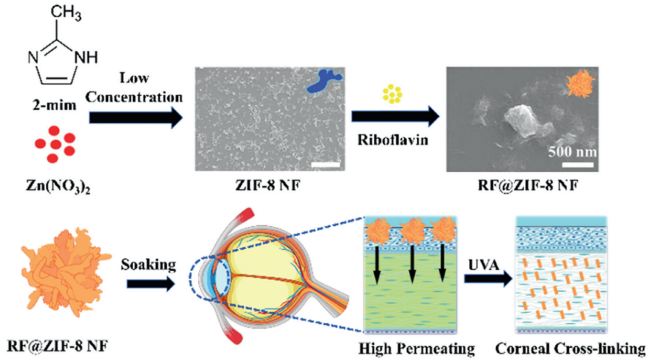

Fig. 1. Scheme of RF@ZIF-8 used for transepithelial treatment of keratoconus. Copied with permission [5]. Copyright 2022, Wiley-VCH.

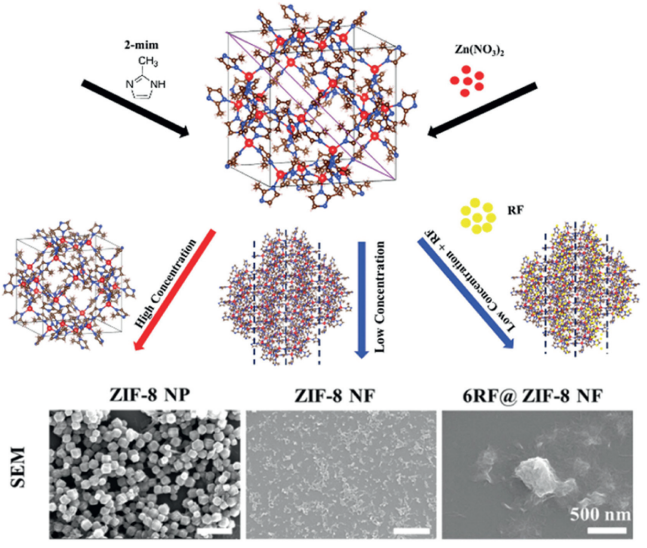

Fig. 2. The morphology control of ZIF-8 NP, ZIF-8 NF, and RF@ZIF-8. Copied with permission [5]. Copyright 2022, Wiley-VCH.

and zinc ions (Zn^{2+}), offering new perspectives in the field of supramolecular chemistry. By adjusting the synthetic conditions, the researchers were able to produce ZIF-8 nanomaterials with distinct morphologies (Fig. 2). The formation and ultimate morphology of the ZIF-8 crystal structure are influenced by the

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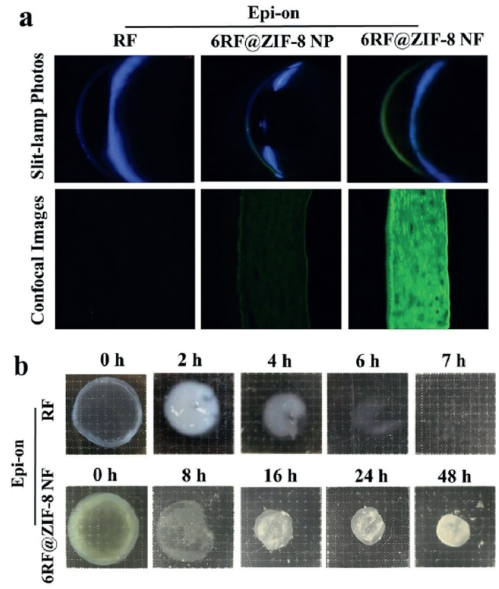

Fig. 3. (a) High permeability of RF@ZIF-8 to rabbit corneal stroma. (b) Crosslinking therapy of 6RF@ZIF-8 on rabbit corneal stroma. Copied with permission [5]. Copyright 2022, Wiley-VCH.

concentration of raw materials and reaction conditions. When the concentrations of zinc nitrate ($Zn(NO_3)_2$) and 2-mim in the reaction solution were increased, they can promote the formation of ZIF-8 nanoparticles until there is sufficient raw material to facilitate crystal growth. However, when the concentrations of these raw materials are extremely low, ZIF-8 exhibited irregular shapes (ZIF-8 NF), possibly because the raw materials were quickly consumed at the initial stage of the reaction, obstructing the normal growth of crystals.

Researchers have utilized this mechanism to control the coordination effect of the system by adding RF, resulting in the preparation of hibiscus-like nanoparticles (6RF@ZIF-8 NF). Specifically, the phosphate ions (PO_4^{3-}) contained in RF can form coordination bonds with the Zn^{2+} in ZIF-8, such as phosphorus-oxygen and oxygen-zinc bonds. This interaction can cause nanoflakes to aggregate into clusters, thereby affecting the final morphology of the RF@ZIF-8 composite material, forming a hibiscus-like structure RF@ZIF-8 NF.

Fluorescence quantification provides technical support for characterizing the permeability performance of RF@ZIF-8 NF in rabbit corneas. After pre-soaking rabbit corneas with RF@ZIF-8 NF for 30 min, photographs and fluorescence images of the corneal tissue (central 5 mm) were captured. A green band was visible within the cornea, which means that RF penetrated into the stromal layer of the cornea (Fig. 3a). Optimal brightness within the corneal stroma was achieved with an RF concentration of 6 mg/mL in the 6RF@ZIF-8 NF formulation. This observation indicates that the green fluorescence signal emanating from the corneal tissue was amplified in tandem with the RF concentration, peaking at 6 mg/mL. This suggests that unique structure of 6RF@ZIF-8 NF allowed it to have a larger contact area with epithelial cells compared to individual nanoparticles, making the penetration efficiency of 6RF@ZIF-8 NF superior to that of 6RF@ZIF-8 NP in the cornea.

Corroborated by corneal enzymatic dissolution experiments (Fig. 3b), the use of the 6RF@ZIF-8 NF for CXL therapy has demonstrated an ability to enhance corneal biomechanical properties more effectively than traditional methods. Within 48 h, the material facilitated a reduction of the residual corneal area to 16%, while maintaining a high concentration of riboflavin. This may mitigate the risk of photodamage caused by epithelial curettage, indicating significant potential for clinical application.

Professors Xingtao Zhou, Jinhai Huang, Rongrong Gao and colleagues effectively surmounted the drug delivery barrier presented by the corneal epithelium, achieving efficient penetration of therapeutic agents into the corneal stroma. This approach elevates keratoconus treatment to a new pinnacle, eschewing the side effects associated with epithelial debridement in conventional procedures. It demonstrates the tangible potential of this strategy in the treatment of corneal diseases, signaling a significant advancement in ocular therapeutics.

The clinical treatment for keratoconus remains relatively primitive, primarily relying on surgical debridement of epithelial cells and high-intensity ultraviolet radiation. This rudimentary approach, attributed to the low permeability of pharmaceutical molecules and the unclear mechanisms of treatment, often imposes a significant psychological burden and severe postoperative complications on patients. Although supramolecular nanotechnology offers a promising new direction for surmounting the corneal epithelial barrier in keratoconus, research might be more focused on meeting clinical needs, specifically the development of a non-invasive pharmaceutical treatment strategy, which should ideally be independent of artificial light sources or, at most, harness natural light catalysis, thereby providing an effective and less invasive means to mitigate the complexities of keratoconus.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Wenlong Li: Writing – original draft. **Feishi Shan:** Writing – original draft. **Qingdong Bao:** Writing – review & editing. **Qinghua Li:** Writing – review & editing. **Hua Gao:** Supervision. **Leyong Wang:** Writing – review & editing, Supervision.

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