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An adhesive hydrogel for the treatment of oral ulcers

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ABSTRACT

Oral ulcers are a common ulcerative injury that occurs in the oral mucosa. When occurring, they can cause mucosal pain and affect eating and communication. The oral cavity, characterized by its moist environment and constant movement of the lips and tongue, presents challenges for conventional drug delivery systems due to its suboptimal adhesion. Therefore, there is a need for the development of adhesive materials specifically designed for use within the oral cavity. In this research, a sticky coacervate incorporating tea polyphenols (TP) was formulated based on the adhesive properties observed in sandcastle worms. The coacervate is composed of Pluronic F68 (F68) and TP, synthesized through the coacervation reaction. The F68-TP coacervates are attached to porcine skin easily. It also reduces bacterial viability and has the ability to clear reactive oxygen species. In animal ulcer models, these coacervates demonstrate anti-inflammatory effects and enhance collagen and muscle fiber synthesis. Overall, these adhesive coacervates with antioxidative and antibacterial properties hold potential as a therapeutic option for oral ulcers in the oral cavity.

Inadequately treated oral ulcers cause impaired speech and mastication in patients [1]. Local treatment options for such conditions typically involve chlorhexidine, dexamethasone solutions, and lidocaine gel [2]. Chlorhexidine solution has spectral antibacterial effects, but its retention time in the oral cavity is short. Lidocaine gel is a local anesthetic with an analgesic effect and weak antibacterial effect. Dexamethasone patch is a steroid drug that regulates immunity but has weak antibacterial ability. Nevertheless, the dynamic nature of the oral cavity, characterized by frequent movements of patients' lips and tongue and high moisture levels, presents challenges for effectively managing oral mucosal diseases through local interventions [3].

The ideal oral mucosal repair material should be thin and elastic with a certain degree of adhesion in a humid environment [4,5]. Researchers have recently been committed to developing biological adhesives [6-9]. Hydrogels can cover the damaged area for more than 24 h, effectively protecting the area from the impact of the complex oral environment [10,11]. As a strategy, adhesive coacervates driven by electrostatic interactions between oppositely charged components were first investigated [12,13]. This type of bonding firmly adheres to the interface by forming ionic bonds, hydrogen bonds, hydrophobic interactions, *etc*. [14].

F68 is used as an emulsifier, defoamer, solubilizer, surfactant, and antibiotic wetting agent [15-17]. Due to its nontoxic and surface-activate properties, F68 has been applied in skin tissue engineering, wound excipients, drug delivery, and antibacterial fields [18-20].

Tea polyphenols (TP) are active phenolic compounds extracted from green tea. They exhibit antioxidant, anti-inflammatory, and antibacterial effects, and have specific therapeutic effects on various pathological processes [21,22]. The antioxidant effect of TP is attributed to its ability to quench free radicals or remove reactive oxygen species (ROS) [23]. TP also possesses inherent adhesive properties and is commonly used as an additive in drug formulations [24,25].

In this study, we selected two oppositely charged components, TP and F68, to prepare adhesive coacervates. They can accelerate the healing of oral mucosal ulcers and have the potential for the treatment of oral ulcers (Scheme 1).

Initially, the F68 aqueous solution and TP aqueous solution were mixed in a volume ratio of 1:1 and then centrifuged at 2000 r/min for several minutes. The coacervates were obtained at the bottom of the centrifuge tube (Fig. S1a in Supporting information). In addition, different proportions of F68 and TP were mixed, and the coacervates exhibited different states. The right side of the di-

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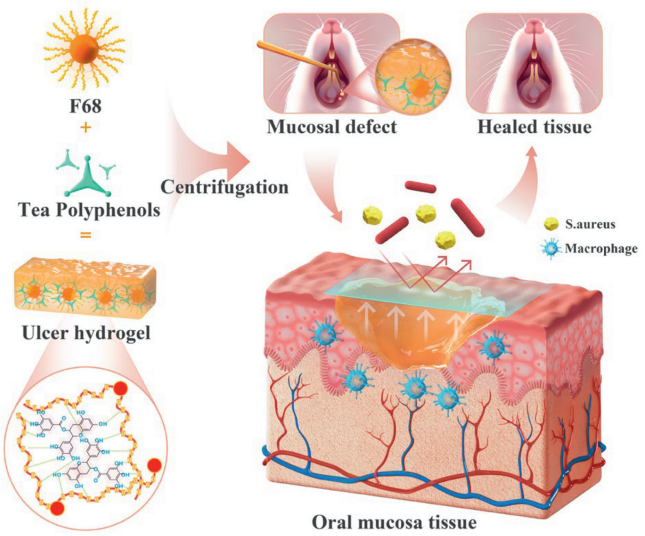

Scheme 1. The application of F68-TP coacervates facilitates the healing of oral ulcers by preventing bacterial growth, eliminating reactive oxygen species, and reducing inflammation.

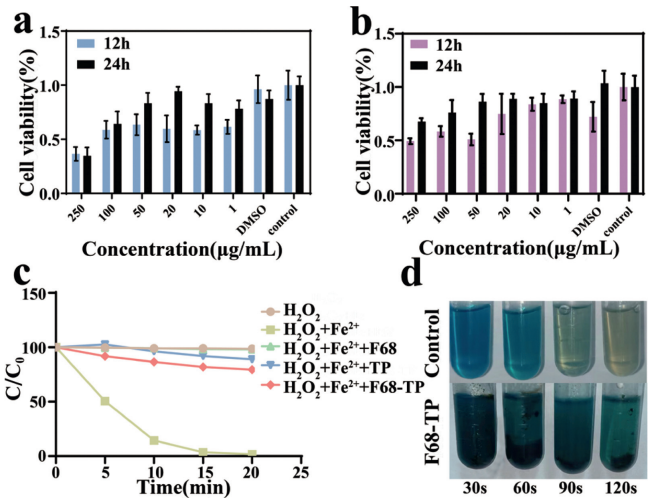

Fig. 2. Cytocompatibility and antioxidant efficacy of the coacervates. (a) 3T3 cell viability with the F68-TP coacervates. (b) HUVECs cell viability with the F68-TP coacervates. (c) The degradation rate of methylene blue. (d) Color change of methylene blue with or without coacervates. Data are presented as mean ± standard deviation (SD) ($n = 3$).

agonal represents the coacervates (Fig. S1b in Supporting information). Subsequently, the molecular interaction of the TA-F68 coacervate was investigated by Fourier transform infrared (FTIR) spectroscopy (Fig. 1a). The stretching vibration of the hydroxyl groups (-OH) in TP shifted after coacervation with F68, which was attributed to the formation of intermolecular hydrogen bonds between the hydroxyl groups of TP and the etheric oxygens of F68. Hydrogen bonds were formed between the hydroxyl and carbonyl groups of TP [26].

The rheological properties of the coacervates were analyzed using an MCR102e rheometer (Anton Paar, Austria). 5%, 10%, 15%, and 20% weight percent TP and 5%, 10%, 15%, and 20% weight percent F68 were mixed with a volume ratio of 1:1. The F68-TP coacervates exhibited high viscosity (10,000 mPa s), which demonstrated robust intermolecular interactions between F68 and TP (Fig. 1b). The adhesion properties of the coacervates were assessed at room temperature using an Instron 5565 tensile testing machine (Instron, America). The adhesion strength was determined by uniformly pulling porcine skin at 1 mm/min. The porcine skin was trimmed to dimensions of 10 cm in length, 5 cm in width, and 1 cm in thickness. The tensile forces applied to 10% and 15% of the coacervates while sliding at a uniform speed were approximately 0.6 N. The maximum adhesion potential of the coacervates reached 12 kPa due to their high adhesion (Fig. 1c). The process of pulling porcine skin by the tensile testing machine is displayed in Fig. 1d.

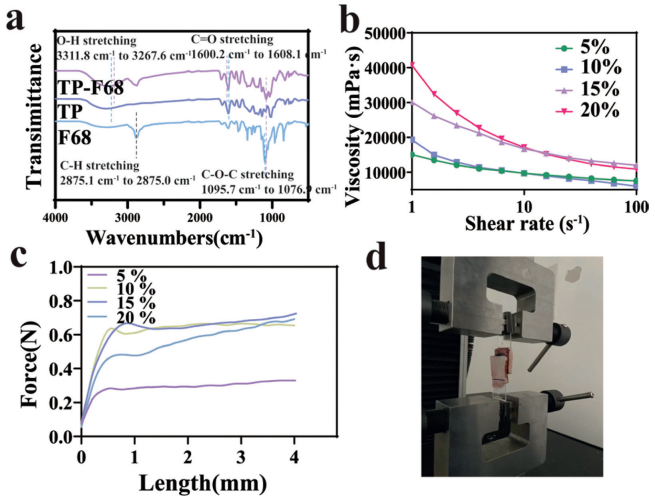

Fig. 1. Exploration of the properties. (a) FTIR spectra of F68-TP coacervates, F68 and TP. (b) Viscosities of F68-TP coacervates. (c) Adhesion between coacervates and the poring skin. (d) Tensile testing machine.

To evaluate the effect of the coacervates on cell behaviors, we used 3T3 fibroblasts and human umbilical vein endothelial cells (HUVECs) as models. As F68-TP coacervates are insoluble in water, they were first dissolved in DMSO and added to plates containing 3T3 cells and HUVECs. As shown in Figs. 2a and b, when the concentration of coacervates was high (100–250 μg/mL), the cell viability after 24 h was approximately 50%. When the concentration was low (<50 μg/mL), the viability of the 24 h cells was approximately 90%. Since the coacervates were insoluble in water, they could be assumed to have less effect on the cells.

Excessive reactive oxygen species could cause cellular damage, which might adversely affect the recovery of wound tissue [27,28]. Methylene blue (MB) could react with ROS, which resulted in degradation. The ROS clearance rate of the coacervates was determined by monitoring the color change of the MBs. The degradation rate of MB in the H_2O_2-Fe^{2+} group was the greatest after 20 min due to the absorption of ROS by MB in Fig. 2c. After 120 s, the degradation of MB with F68-TP coacervates decreased in Fig. 2d. The results demonstrated that the F68-TP coacervates had antioxidant potential.

Bacterial invasion is a common cause of wound infection [29,30]. The mortality of *Staphylococcus aureus* (*S. aureus*) following treatment with the F68-TP coacervates is shown in Fig. S2a (Supporting information). After 10^4-fold dilution, the number of colonies in the control group was approximately 10^3 colony forming units (CFU)/mL. *S. aureus* was hardly detected in the coculture group treated with F68-TP. F68-TP coacervates spread at the bottom of the 96-well plates were able to kill more than 99% of *S. aureus* strains in the range from 10^6 CFU/mL to 10^7 CFU/mL. The antibacterial zones of the coacervates combined with the drug sensitivity test paper are shown in Fig. S2b (Supporting information). The bacterial concentration on the plate was 10^8 CFU/mL. The diameter of the antibacterial zone loaded with F68-TP was 19 mm for *S. aureus*. The blank group and F68 group did not exhibit sig-

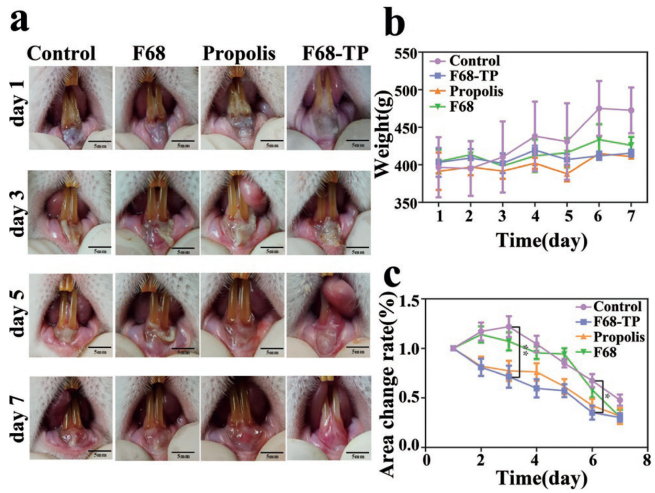

Fig. 3. Application of F68-TP coacervates for promoting oral ulcer healing in the rat model. (a) Macroscopic images of oral ulcers. Scale bar: 5 mm. (b) Body weights of the rats throughout the treatment. (c) Analysis of the ulcer wound area. $^{*}P < 0.05$, $^{**}P < 0.01$. Data are presented as mean ± SD ($n = 5$).

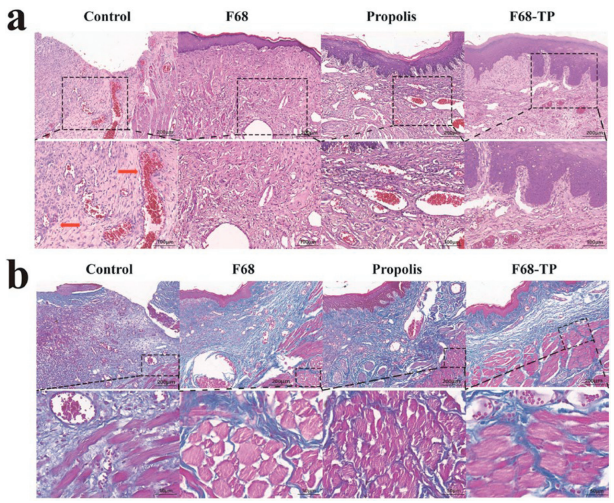

Fig. 4. (a) H&E staining on day 7 after treatment (the red arrow indicates a blood vessel). Scale bars: 200 μm and 100 μm. (b) Masson's trichrome staining on day 7 after treatment. Scale bars: 200 μm and 50 μm.

nificant antibacterial zones. The results demonstrated that F68-TP coacervates had good inhibitory effects on *S. aureus*.

The *in vivo* bioeffects of F68-TP coacervates were studied using a chemical-induced oral ulcer model (Fig. 3). Animal experiments were approved by the Ethics Committee of West China Hospital of Stomatology, Sichuan University. The body weight of the rats in the blank control group showed a decreasing trend from day 1 to day 3, which might be related to the pain of oral ulcers hindering feeding in the rats, which led to a decrease in body weight. The body weight of the F68-TP group changed slightly, indicating that the coacervates alleviated ulcer symptoms. The ulcer area was measured to more intuitively reflect the severity of the ulcers. As shown in Fig. 3b, the ulcer area in the propolis group and F68-TP group began to decrease from day 1 until day 7. The average ulcer area on day 1 was A_1, and the average ulcer area on day i was A_i. Thus, the area change rate was A_i/A_1. Finally, compared with that in the initial state, the ulcer area in the propolis group and F68-TP group decreased by approximately 69%. In contrast, compared with that on day 1, the ulcer area in the blank control group was 21.9% greater in Fig. 3c. After day 6, the ulcer gradually healed. Moreover, the oral ulcers were monitored after treatment, and the images were shown in Fig. 3a. On day 1, gray necrotic tissue covered the surface of the gums and was subsequently covered with a pseudomembrane. The pseudomembrane gradually fell off during the healing process, and white spots could be observed on the gingiva [31]. The results indicated that F68-TP coacervates could reduce ulcer inflammation and promote healing. Inflammatory regulation was critical for tissue ulcer recovery.

Upon sacrifice, rats were used to collect gingival mucosa samples surrounding the ulcer for histopathological morphology evaluation, as illustrated in Fig. 4. Within the control group, a notable infiltration of granulation tissue was observed within the mucosal epithelium (Fig. 4a). This tissue exhibited an abundance of lymphocytes and red blood cells, with a lack of complete formation of epithelial tissue on the mucosa. Conversely, a reduced presence of inflammatory cells and red blood cells was noted. In the group that received F68 and propolis treatment, both epithelial tissue and stratum corneum were identified. Notably, significant recovery of blood capillaries and basal lamina was evident in the F68-TP treatment group. Moreover, Masson's staining results further supported these findings (Fig. 4b). Following treatment with F68-TP coacervate, the collagen deposition surrounding the ulcer exhibited denser organization on day 7. The mature stratum corneum was observed in the epithelial tissue, accompanied by more robust muscle fibers. These observations suggest that F68-TP coacervate could serve as a promising candidate for ulcer healing.

Oral ulcers can affect patients' mental health and reduce quality of life [32,33]. Coacervates exhibit both antioxidant and antibacterial effects to fulfill the demands of oral ulcer repair [34]. Conventional drugs for oral ulcers have antibacterial and anti-inflammatory effects, but their efficacy can be compromised due to the unique characteristics of the oral environment, which makes it difficult for ulcer patches, gels, and other drugs to adhere to the buccal mucosa [35-37]. In this study, we developed an adhesive coacervate to promote ulcer healing. The results indicated the promising potential of the product, suggesting that it could be further developed as an injectable gel to promote ulcer healing.

In conclusion, we have developed unique coacervates specifically formulated to promote tissue adherence and aid in the healing of ulcer wounds. Our F68-TP coacervates have displayed antibacterial and antioxidant qualities compared to current clinical medications. Our research indicates that the F68-TP coacervate plays a role in tissue healing by reducing inflammation, suppressing bacterial growth, and promoting the formation of muscle fibers and collagen. These findings highlight adhesive coacervates have potential commercial applications in developing novel therapies for oral ulcers.

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.

CRediT authorship contribution statement

Xi Chen: Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Investigation, Formal analysis. **Xue Zhang:** Writing – review & editing, Visualization, Supervision, Software, Resources, Methodology, Investigation, Data curation. **Shuai Yang:** Writing – review & editing, Validation, Software, Methodology, Investigation, Formal analysis. **Jie Wang:** Software, Resources, Methodology, Investigation. **Tian Tang:** Writing – review & editing, Funding acquisition, Formal analysis, Conceptualization.

Maling Gou: Writing – review & editing, Methodology, Funding acquisition, Formal analysis, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.110021.

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