

CROSSLINKS AND CONNECTIONS: THE STICKY SIDE OF GELATIN

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Have you ever wondered how dosage forms, such as films or gels, manage to stick to the moist surfaces of the mouth or eyes without simply sliding away? The answer lies in a fascinating phenomenon known as mucoadhesion [1]. This process involves getting a material to adhere to mucosal tissue long enough to achieve its intended purpose, particularly in drug delivery systems designed to release therapeutic agents in a controlled manner. Among the many biomaterials explored for this purpose, gelatin stands out due to its excellent biocompatibility, versatility, and modifiable chemistry [2].

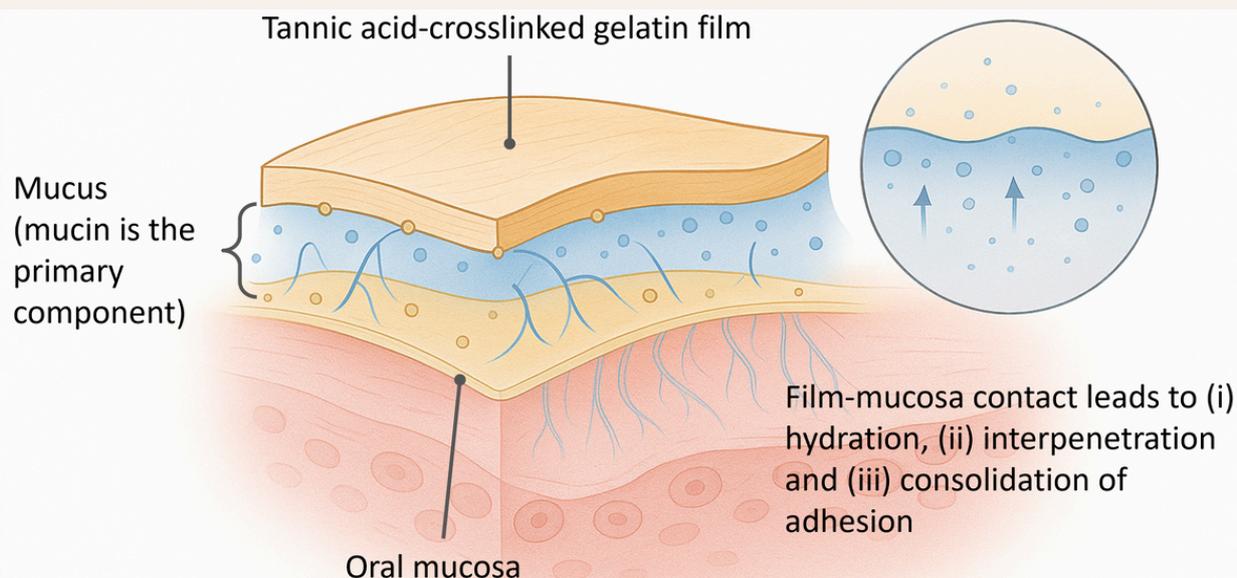
GELATIN WITH A SCIENTIFIC TWIST

Gelatin is not a new substance. It is the same biopolymer that gives jellies their familiar wobble. However, in pharmaceutical research, it plays a far more sophisticated role. Derived from collagen, gelatin is rich in functional groups such as hydroxyl, carboxyl, and amine, which enable a range of interactions with biological molecules [2].

When hydrated, gelatin swells and exposes these reactive sites, ready to interact with the negatively charged mucin layer that coats mucosal tissues, including those in the oral cavity, eye, and colon. These interactions involve hydrogen bonding, van der Waals forces, and polymer chain interpenetration, mechanisms that collectively allow gelatin to anchor effectively to mucosal surfaces. However, native gelatin has limitations.

It hydrates rapidly and loses structural integrity under physiological conditions, which restricts its adhesive performance. Crosslinking offers a way to reinforce the gelatin network and extend its mucoadhesive action.

CROSSLINKING WITH PURPOSE



Our research team has been exploring tannic acid, a plant-derived polyphenol, as a natural crosslinker to develop a more resilient gelatin matrix. When introduced to gelatin, tannic acid interacts with amine and hydroxyl groups along the gelatin chains, forming a stable crosslinked network that enhances structural integrity and reduces premature dissolution [3]. Beyond reinforcing the gelatin matrix, tannic acid also serves as an adhesive promoter.

Phenolic-based adhesives inspired by marine organisms such as mussels have been extensively studied in biomaterial science. However, their application in mucoadhesive drug-delivery systems, particularly for buccal formulations, remains relatively underdeveloped. Tannic acid contains pyrogallol moieties that resemble catechol [3], the functional group responsible for the strong underwater adhesion of mussel adhesive proteins (MAPs) [4]. Catechol groups can form covalent bonds with thiols and amines present in human mucin, facilitating

firm attachment to moist biological surfaces. By analogy, tannic acid may partially mimic this natural adhesion strategy, strengthening the mucoadhesive interactions between gelatin and mucosal tissue. This dual functionality, which simultaneously reinforces mechanical performance and promotes surface adhesion, makes tannic acid an attractive modifier for biomedical applications. In our recent publication in *Biopolymers*, we reported that bovine gelatin films crosslinked with tannic acid achieved a 1.6-fold increase in mucoadhesive strength and exhibited an extended dissolution time of up to 6 hours, compared to non-crosslinked films, which dissolved within approximately 6 minutes [5]. The crosslinked films also exhibited substantial water uptake, improved mechanical resilience, and measurable antioxidant activity within the first two hours of exposure to moist environments, all of which support prolonged mucosal residence and stable drug release.

BEYOND THE BUCCAL CAVITY

While our current work focuses on buccal film systems for sustained drug delivery, the gelatin-tannic acid platform opens new opportunities beyond the oral cavity. It could serve as a bioadhesive system for nasal, ocular, and dermal applications or as a component in wound dressings, implant coatings, and tissue engineering scaffolds. By tailoring the degree of crosslinking and key formulation parameters, we can tune adhesion time, swelling behaviour, and drug-release profiles to meet diverse clinical needs.

Building on these findings, our research team has secured a 2024 Fundamental Research Grant Scheme (FRGS) award from the Ministry of Higher Education (FRGS/1/2024/SKK16/UITM/02/1) to investigate the underlying mechanisms governing mucoadhesive attachment between tannic acid-crosslinked gelatin and mucosal surfaces. This project aims to establish a mechanistic framework that integrates multiple factors contributing to interfacial adhesion. Specifically, it examines how both the modified gelatin matrix and mucosal surface morphology influence adhesion, while rheological and viscoelastic properties are assessed to understand their roles in the spreading and interpenetration phases of attachment. Adhesive performance will be comprehensively evaluated by quantifying tensile and detachment strengths under simulated physiological conditions. In addition, the study explores chemical and interfacial dynamics, including crosslink density and potential charge interactions at varying pH to provide molecular-level insights into the adhesive behaviour of this natural polymer system.

The outcomes are expected to clarify how crosslinked natural polymers behave at biological interfaces, providing essential guidance for the rational design of next-generation bioadhesive systems.



A SUSTAINABLE STEP FORWARD

The exploration of gelatin-tannic acid systems demonstrates that “stickiness” in science is anything but simple. It is shaped by a delicate balance of chemistry, physics, and biology, and when these elements are carefully tuned, they can transform a common biomaterial into a smart, responsive delivery platform. As our research progresses, the vision remains clear: to develop eco-sustainable, biocompatible systems that not only adhere where needed but also protect, heal, and release therapeutic agents with precision.

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