Development of Polymer-based Drug Delivery System for Wound Healing

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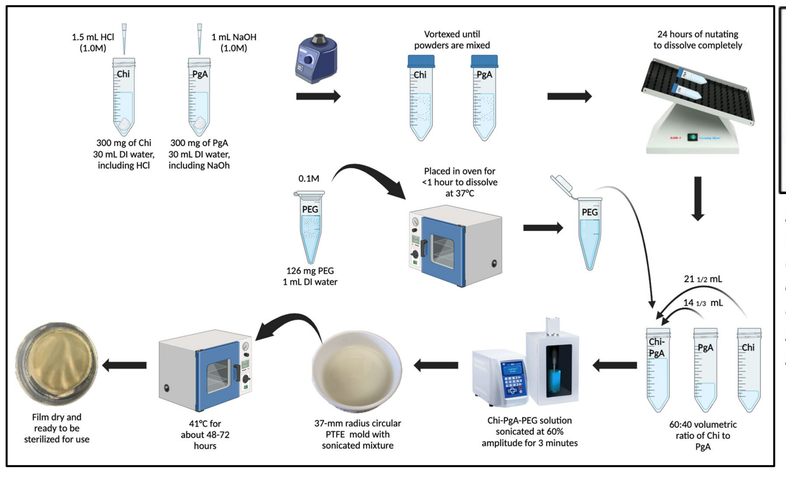
Abstract

Skin is the largest organ in the human body that provides a barrier against external stresses. However, during this protection system, it can become susceptible to wounds caused by trauma or chronic conditions such as diabetes and spinal cord injury (SCI). Chronic wound closure and skin regeneration are worldwide problems and treating acute and chronic wounds (for instance, diabetic wound ulcers and SCI) can cost up to $31.7 billion annually in the US alone.[1] As the wound healing systems are evolving, an ideal system should (1) augment cell proliferation and enhance the wound healing efficiency by expediting the wound closure rate, (2) be biocompatible (3) possess antibacterial properties (4) maintain its presence at the wound bed for ample duration to facilitate comprehensive healing[2]. Our intention here is to develop a wound dressing, polyelectrolyte complex (PEC) film[3], for chronic wounds that incorporates new compounds known for their participation in recruiting more cells to the wound bed for wound management in the early and late phases of wound healing[4]. These new compounds, elastin-like proteins (ELP), are known for acting as carriers to various peptides (employed for their biological activity in wound healing)[5]. ELP incorporation aims to achieve a single-application method coupled with slow release of these nanoparticles to ensure their availability for the entire wound healing cycle and prevent them from degradation due to proteases. Another aspect targeted here is the biodegradability of the PEC film used to ensure the availability of the film during the entire wound healing process to fulfill the requirement of following a single-application approach.

Materials and Methods

For these studies, a reproducible approach was employed for the synthesis of the films using different ratios of natural biomaterials such as chitosan, polygalacturonic acid (PgA), and polyethylene glycol (PEG) as per our published protocol of PEC with modification[3-4]. A variety of compositions, pH, temperature, and duration were used to cast the PEC films in film production to achieve polymer-based film with optimum biodegradability and nanoparticle release. The films were manufactured using these biomaterials with or without encapsulation with different elastin-like polypeptides (ELP) fused bioactive molecules or growth factors necessary for wound healing processes. The solution was then poured into Teflon containers in an oven at 40°C for 2-3 days (or until the films dried). Scanning electron microscope (SEM) imaging was done to locate the nanoparticles in the films. The films were cut into 10 mm disks and were stored in 24-well plates in PBS solution to mimic the wound environment. Each film disk was studied for degradation (by measuring its thickness and weight over 35 days). Another 24-well plate carrying 10 mm film disks with nanoparticles in PBS solution was stored in an incubator at 37°C on a shaker rotating at 500-1000 rpm. PBS solution samples (in which the films were stored) were collected over 7 days for staining and western blot to quantify the nanoparticles released during the study.

PEC-PEG Film Manufacturing and Encapsulating Nanoparticles



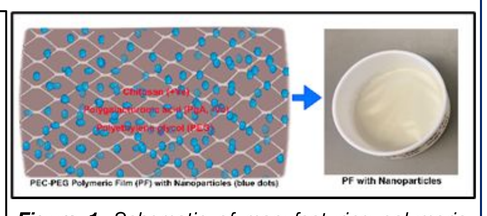


Figure 1. *Schematic of manufacturing polymeric film (PF) consisting of natural biomaterials such as chitosan, PgA, and PEG (left). Schematic of PF embedded with multifunctional nanoparticles (blue dots). Right side image of PF film containing nanoparticles in container that we prepared in our laboratory at Rutgers University.*

Scanning Electron Microscopy of PEC Films

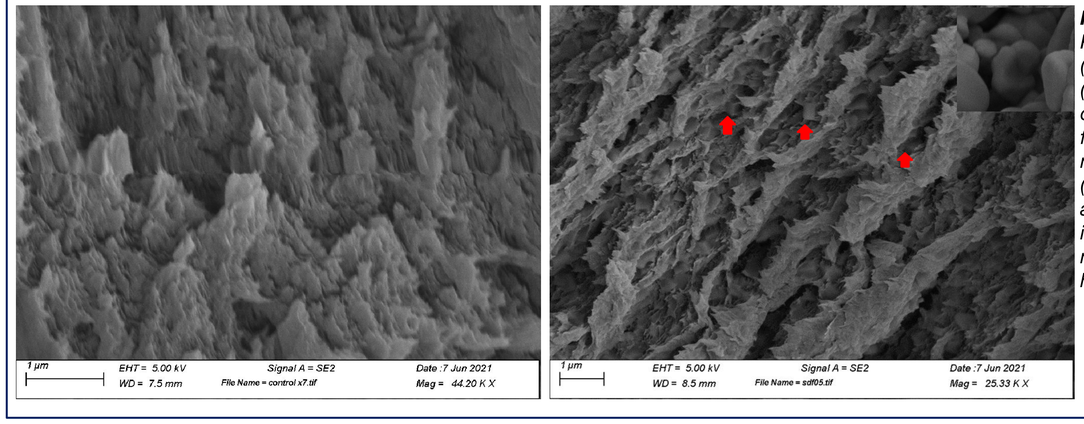


Figure 2. *SEM of PEC films without (left) and with (right) stromal cell derived factor fused with ELP nanoparticles (SDF-ELP; red arrows). Inset image of SDF-ELP nanoparticles in high magnification.*

Results

Swelling and Degradation Profile of PEC and PEC-PEG Films

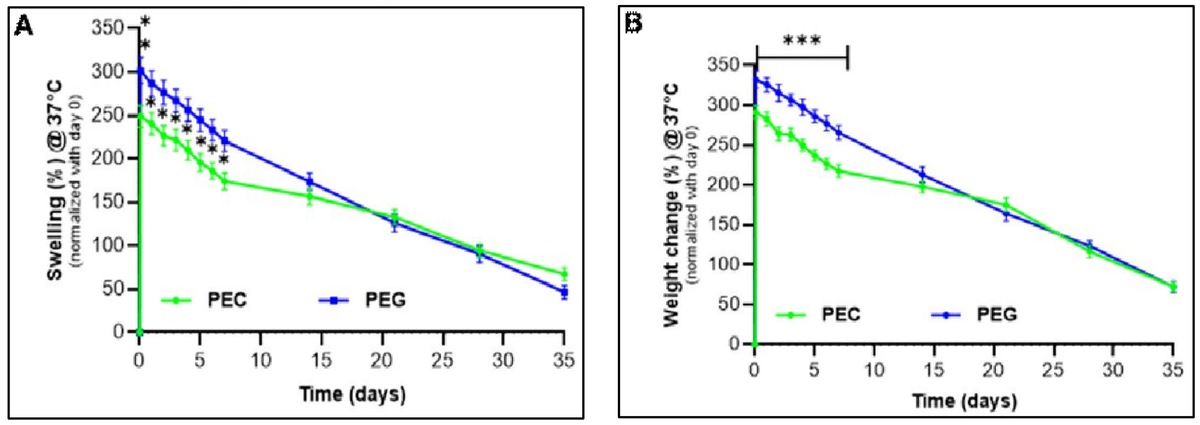


Figure 3. Swelling and degradation profiles of the PEC and PEG wound dressings at 37°C. *Data was transformed into % change of swelling profile (**A**) and weight change (**B**) over time after being normalized with day 0 measurements of dry films (3 independent experiments using 3 different batches of films). Data is represented as the mean ± SEM (n=11/group). Statistical analysis was done using two-way ANOVA followed by Tukey's HSD multiple comparison test. * p<0.05, **p<0.005, p*** p<0.0005.*

Nanoparticles Encapsulation into PEC Film and Staining

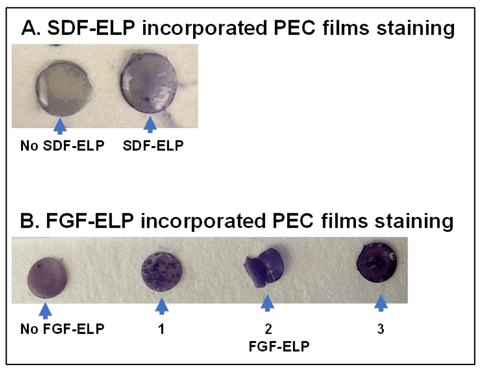


Figure 4. Incorporating and identifying the encapsulation of nanoparticles into PEC film. *The goal of this study was to identify whether the PEC film would be a good candidate for the delivery of drug packaged nanoparticles such as ELP, stromal-derived factor-1, and fibroblast growth factor 2 fused with ELP (SDF-ELP and FGF-ELP). We added SDF-ELP or FGF-ELP (1 µg/cm^2) to the chitosan-PgA mixture during PEC film preparation and stained these films with anti-FGF and anti-SDF antibodies to detect incorporated protein nanoparticles. We detected positive staining for nanoparticles demonstrating that they were incorporated into the films (top, 1-sample for SDF-ELP as shown in Fig. A and 3-samples for FGF-ELP in Fig. B) as compared to a control film without nanoparticles (left, 1-sample for control in each Fig. A and B).*

PEC/PEC-PEG Nanoparticles Encapsulation and Release Profile

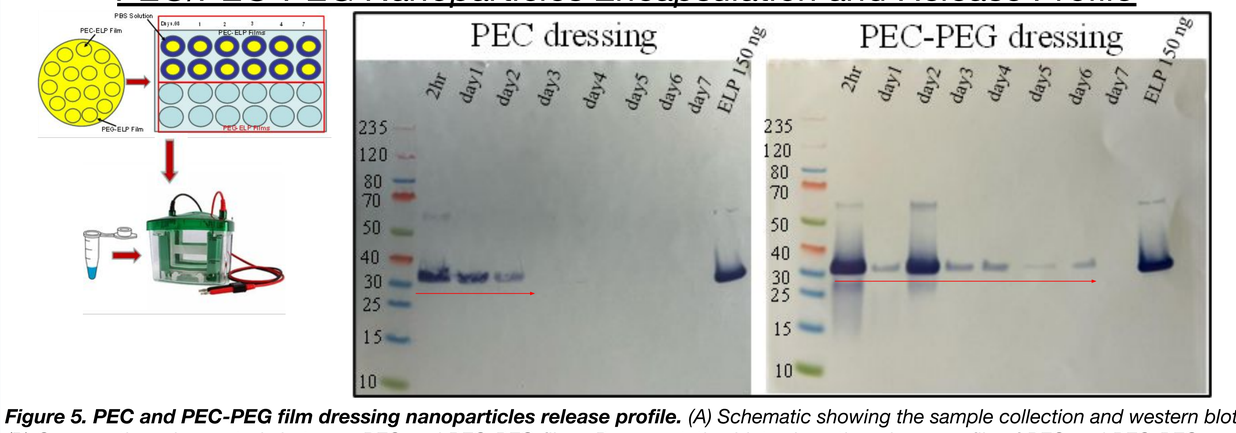


Figure 5. PEC and PEC-PEG film dressing nanoparticles release profile. *(A) Schematic showing the sample collection and western blot. (B) Comparative release study between PEC and PEC-PEG films. Representative blots show the release profile of PEC and PEC-PEG over period of 7 days. The colored bands on western blot suggested graded slow release of ELP nanoparticles over time. Bands on membrane correspond to the molecular weight and align with control ELP sample (last band).*

Conclusions

We developed slow drug delivery system using stable, reproducible conditions to successfully deliver drugs, nanoparticles, and any biological therapeutics to chronic skin wounds with optimum degrading duration. The results will be further confirmed using clinical application on relevant animal models with chronic wounds. The system is biocompatible with reduced risk of irritation or rejection as all the polymers used are either naturally occurring or are currently used for creating wound healing systems.

References

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