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Engineering Extended-Release Profiles for Biologics via Crosslinking of Poloxamer 407 Hydrogels

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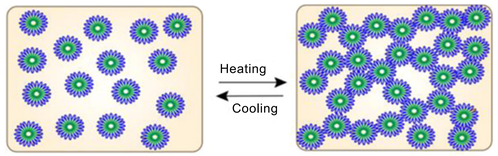
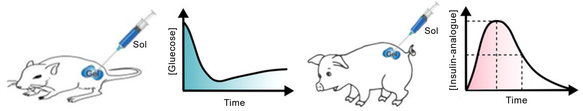
Introduction

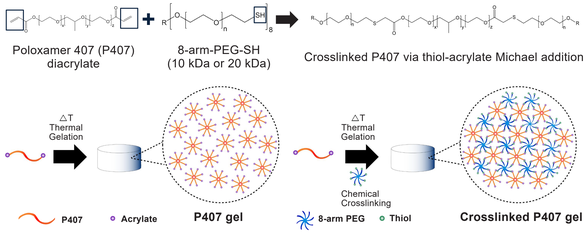
- In situ hydrogels undergo sol-gel transition upon administration, offering a noninvasive approach for biotherapeutics delivery over an extended period
- Poloxamer 407 (P407) is an attractive biopolymer for in situ forming of thermosensitive hydrogels. But its rapid disintegration has limited the therapeutic applications for controlled release over a short period of time
- To further enhance the delivery potential of P407 hydrogels, an in situ crosslinking approach was developed to improve hydrogel stability and enable sustained release profiles of biologics for up to 2 months





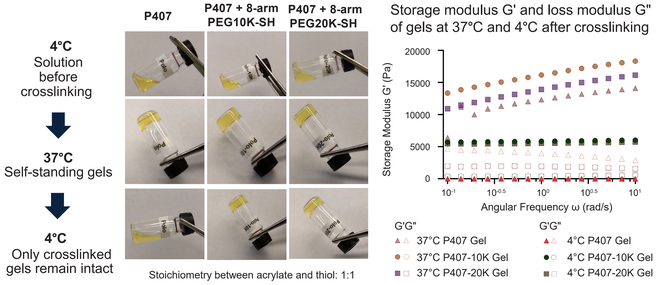
Crosslinking strategy

P407 hydrogel network reinforcement via chemical crosslinking

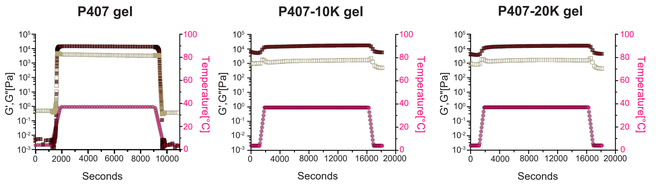


Results

Chemical crosslinking enhances stability of P407 gels regardless of temperature



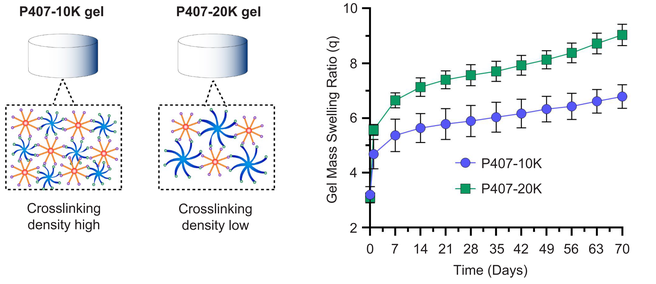
Rheological studies demonstrate crosslinked P407 gels do not revert to solution state at 4°C



Rheology measurement was performed after thermal gelation process at 37°C

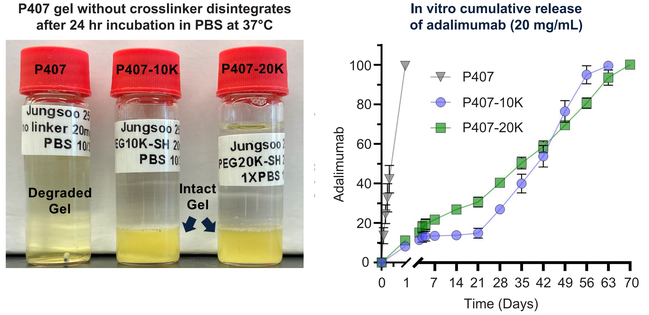
■ G': Storage modulus □ G": Loss Modulus ● °C: Temperature

Gel swelling ratio of crosslinked P407 hydrogels varies, depending on the molecular weight of the crosslinker

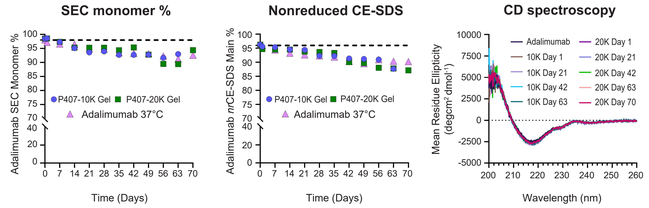


- Crosslinking density ↓ → Gel swelling ratio ↑
- Can expect faster release of biologics in a faster-swelling gel

Crosslinked P407 hydrogels exhibit prolonged release of adalimumab over 2 months

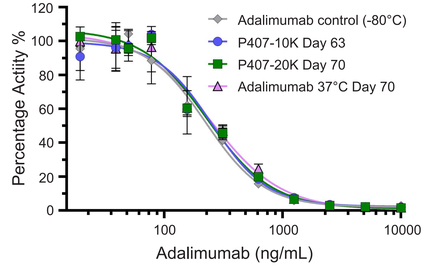


Encapsulation within crosslinked P407 hydrogel did not adversely affect the stability and the secondary structure of adalimumab



Crosslinked P407 hydrogels did not affect the in vitro potency of encapsulated adalimumab

Inhibition profiles of adalimumab by TNF-α: Human TNFR1 blockade competitive enzyme-linked immunosorbent assay (ELISA)



Calculated IC50 values by ELISA

Type	IC50
Adalimumab control	224.2 ± 46.0 ng/mL
P407-10K Day 63	254.1 ± 50.7 ng/mL
P407-20K Day 70	231.0 ± 32.1 ng/mL
Adalimumab 37°C Day 70	249.0 ± 49.3 ng/mL

Conclusions

- Covalent crosslinking with the combination of thermal gelation enhanced P407 hydrogel's stability, enabling extended-release profile up to 70 days compared to non-crosslinked hydrogels (1 day release duration)
- Crosslinked P407 hydrogels did not adversely affect the structural integrity, stability, or in vitro potency of the encapsulated biologics
- This study highlights the impact of crosslinking on mechanical properties and release kinetics of the P407 hydrogel system, offering a promising approach for developing long-acting injectable formulations of biomacromolecules

References

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