

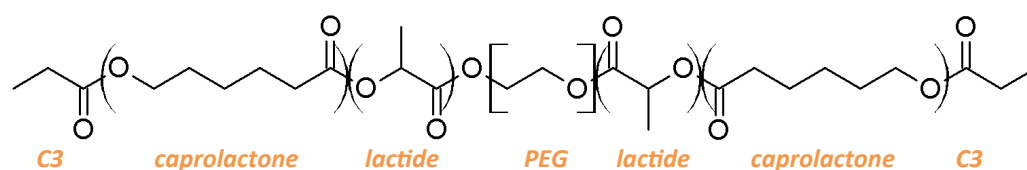
Injectable gels

InGell® is an advanced injectable gel drug depot system, offering un-paralleled retention and release of active pharmaceutical ingredients from a soft, localized drug depot.

InGell technology offers the possibility to create novel drug depot products using bioabsorbable polymers, that can simply be mixed with drug compounds or other therapeutic actives. The drug delivery depot only consists of the active ingredient and the injectable, bio-erodable polymer. There are two polymer sets available:

- ✓ **Gamma** - The polymers dissolve in water and form hydrogels at body temperatures. Upon injection into soft tissues, the polymers rapidly form a soft, macroscopic depot, which physically entraps active ingredients.
- ✓ **Liquid Polymer (LQP)** - LQP is a 100% pure liquid polymer without solvents. Like Gamma, upon injection into soft tissue, it will rapidly form a soft, macroscopic depot, which physically entraps active ingredients.

InGell is based on PCLA-PEG-PCLA tri-block copolymers with aliphatic end groups.

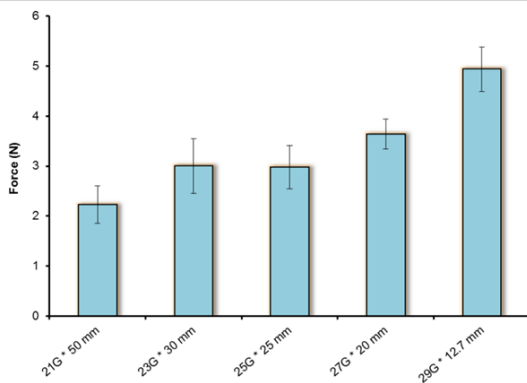
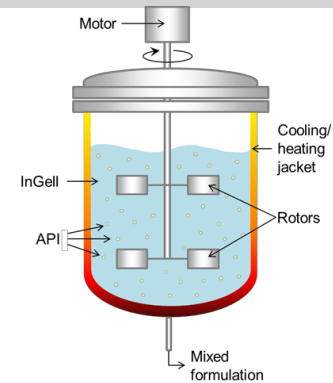


Original compound	Degradation products	Excreted as
Lactide	lactic acid	CO ₂ and H ₂ O
Caprolactone	hydroxy hexanoic acid	hydroxy hexanoic acid
Polyethylene glycol (PEG)	PEG	PEG
Ethyl (endcap)	acetic acid	acetic acid
Propyl (endcap)	propionic acid	propionic acid
Hexanoyl (endcap)	hexanoic acid	hexanoic acid

- ✓ Safe to use polymers
- ✓ Well known building blocks
- ✓ Biodegradable
- ✓ Urinary excretion

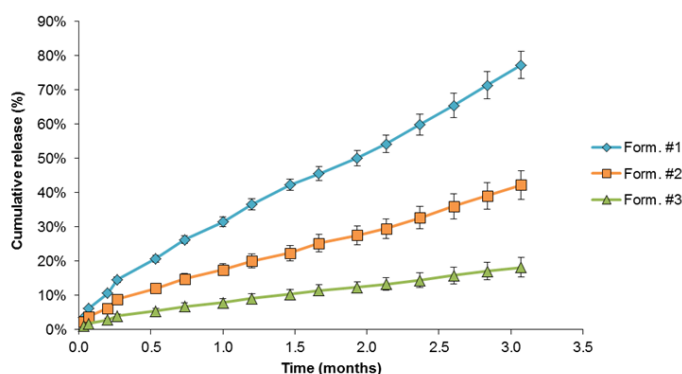
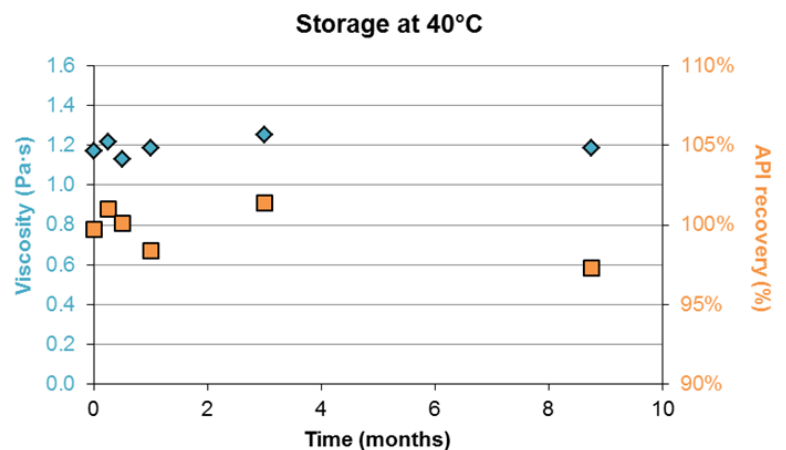
Injectable gels

- ✓ Easy processing by mixing solutions and therefore easy scalable
- ✓ No organic solvents
- ✓ High drug loading capacities (up to 25%)



- ✓ Injectability study performed with 20% hydrogel at ambient temperature
- ✓ Injection speed was 150 mm/min, and force was <6N
- ✓ Injectability through thin needles (30G)

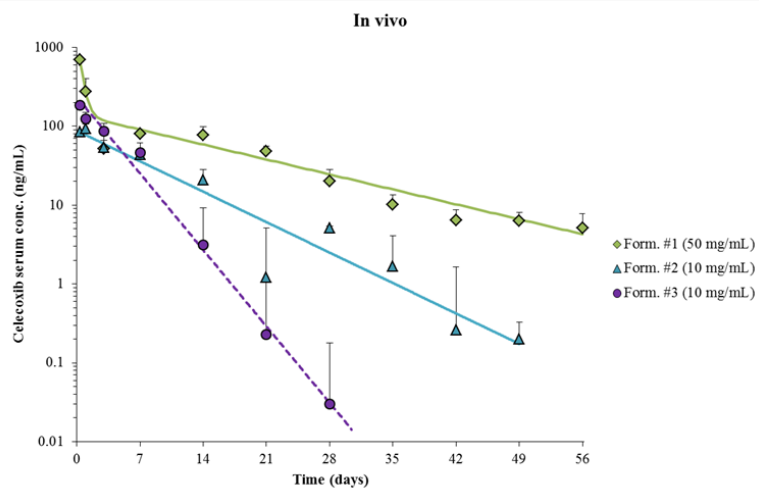
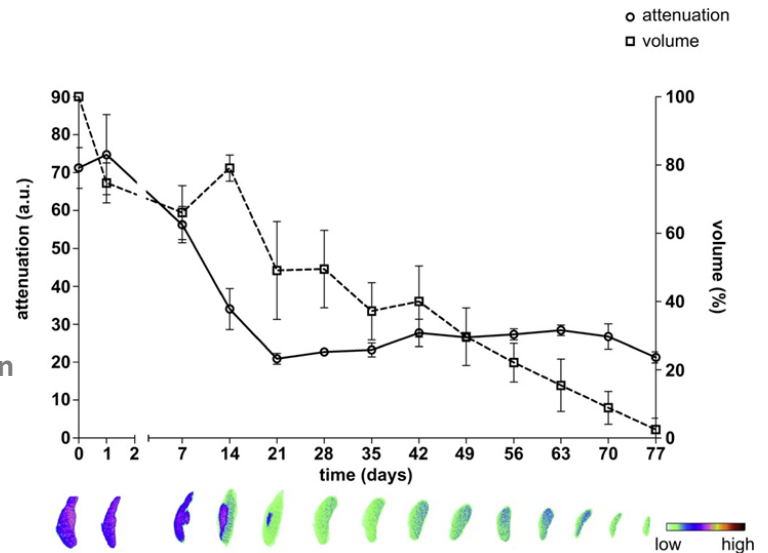
- ✓ Very stable. Even at higher temperatures
- ✓ LQP formulations loaded with 5% IL-2029 (SMD with an aqueous solubility of 3.3 mg/L)
- ✓ Stored at 40°C with intermittent sampling
- ✓ Stable viscosity and stable API recovery for at least 9 months at 40°C!



- ✓ Tunable in vitro releases
- ✓ 3 months sustained release of 7.5% IL-2029 from LQP
- ✓ Different release rates can be obtained by changing the triblock composition and/or endcap
- ✓ Ideal for hydrophobic small molecule drugs (SMDs)

Injectable gels

- ✓ Gel erodes gradually, from outside-in
- ✓ No depot residues left behind
- ✓ Degradation rate depends on triblock composition



- ✓ Sustained in vivo release of hydrogels loaded with celecoxib, subcutaneously injected in rats
- ✓ Injected 500 μ L using 25G needles
- ✓ Different polymers resulted in different release profiles (Form. #2 and #3)
- ✓ 8 weeks in vivo release
- ✓ Hydrogel for Form. #3 completely gone after 8 weeks. Form. #1 and #2 significantly smaller/ degraded

References

- Petit et al., *Biomaterials*, Volume 53, Pages 426-436
- Tellegen et al., *Journal of Tissue Engineering and Regenerative Medicine*,. Accept manuscript: 2017.