innocore 20 YEARS PHARMACEUTICALS

LiQuid-Polymer™

A biodegradable polymer-based long-acting injectable drug delivery platform for lipophilic drug molecules

Brochure

Key attributes:

+ Ready-to-inject liquid dosage form
+ Easy and patient-friendly administration
+ Sustained release for weeks to months
+ Suitable for lipophilic drug molecules
+ High drug doses with small injection volume
+ Biocompatible and fully bioresorbable
+ Manufacturing by standard processes and easy scale-up
+ Stable under ambient storage conditions
+ Storage at room temperature

InnoCore's LiQuidPolymer™ is an advanced biodegradable polymeric drug delivery system for the development of long-acting injectable depots of lipophilic drug molecules. LiQuidPolymer solubilizes otherwise insoluble drugs and offers improved pharmacotherapeutic efficacy over extended periods – from days to months – and increased therapy adherence. The simplicity of the liquid and ready-to-inject LiQuidPolymer system eliminates complicated manufacturing procedures and the need for time-consuming and inconvenient reconstitution procedures prior to administration. The LiQuidPolymer platform is perfectly suited for the development of long-acting injectable dosage forms for the treatment of chronic and site-specific diseases.

API	Aq. solubility (mg/mL)	LogP	Drug loading (mg/mL)
Palonosetron	0.464	2.7	100 - 150
Celecoxib	0.0050	3.5	200 - 250
Terbinafine	0.0007	5.5	200 - 250
Donepezil	0.0045	4.7	70 - 100

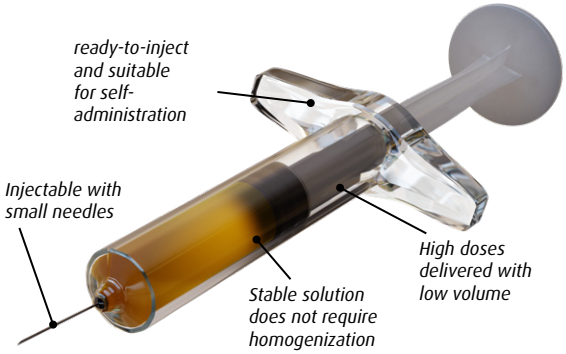
Table 1
Examples of API with low aqueous solubility solubilized by LiQuidPolymers.

LiQuidPolymers enables the development of user-friendly ready-to-inject dosage forms thereby eliminating the need for complicated reconstitution procedures

Ready-to-use dosage forms

A major advantage of LiQuidPolymer is that it allows development of ready-to-use liquid formulations that do not require complicated and time-consuming mixing procedures prior to administration but instead can be immediately administered – FIG 1. LiQuidPolymer does not contain any water or (organic) solvents thereby avoiding premature hydrolytic degradation of the polymer and drug-related stability issues during long-term storage. Consequently, LiQuidPolymer formulations can be stored at room temperature. Critical quality attributes of LiQuidPolymers remain unaffected during long term storage at room temperature and under accelerated storage conditions (40 °C) – FIG 6.

Figure 1
High drug doses delivered with small volumes and small needles. LiQuidPolymer formulations are adapted to prefilled syringes and autoinjectors.



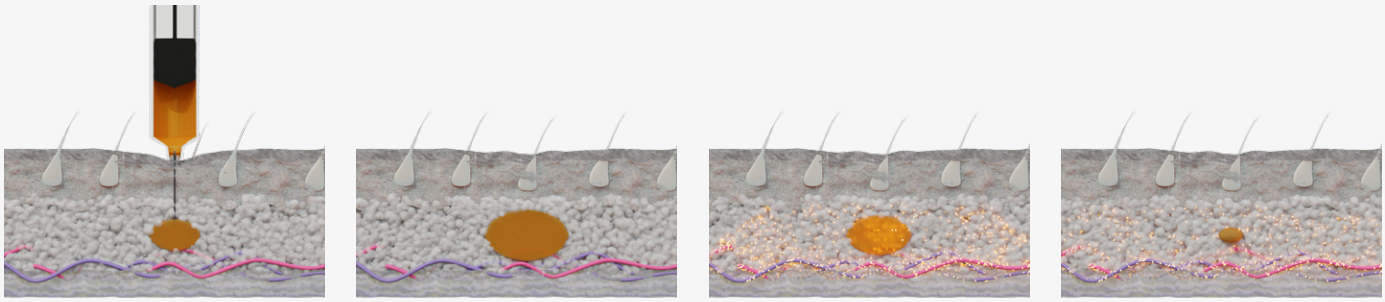
Control over release kinetics

Drug release from LiQuidPolymer is governed by a combination of diffusion and polymer erosion and a range of parameters can be used to modulate the release kinetics – FIG 2. By changing the composition of the polymer, the partition coefficient of the drug molecule, as well as the erosion rate of the polymer depot, are tuned, allowing controlled release from weeks to months – FIG 3. *In vivo* pharmacokinetics of LiQuidPolymer based formulations are characterized by a low burst release followed by sustained diffusion-controlled release for several weeks to months – FIG 4.

High drug doses

LiQuidPolymer effectively solubilizes lipophilic compounds allowing for a significant increase in the dissolution rate and the bioavailability of poorly water-soluble drugs. LiQuidPolymer formulations are prepared by simply dissolving the drug in the liquid polymer. Over 200 mg/ml of lipophilic drug can be solubilized in LiQuidPolymer allowing the administration of up to 500 mg of otherwise water-insoluble drugs via a 2 mL subcutaneous injection – TABLE 1.

Figure 2
Schematic illustration of formation and erosion of LiQuidPolymer depots *in vivo*.



LiQuidPolymer-based dosage form injected subcutaneously

Solid depot is formed in vivo instantly

API is continuously released by diffusion and degradation

Gradual erosion of the depot over time

Figure 3
The composition of the LiQuidPolymers is tuned to achieve target loading and release duration from weeks to months. API-1: 315 g/mol, aq. sol. <1 mg/mL; API-2: 381 g/mol, aq. sol. <3 µg/mL; API-3: 426 g/mol, aq. sol. <3 µg/mL.

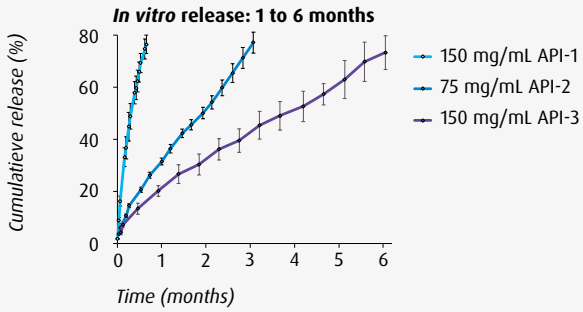
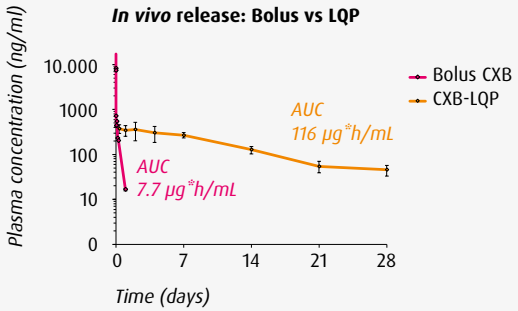


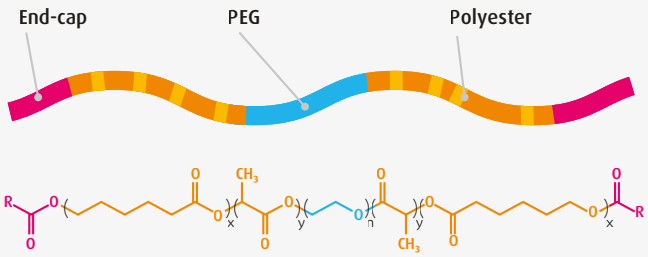
Figure 4
LiQuidPolymers allow sustained release and increased bioavailaibility of small lipophilic molecules increasing the bioavailability. *In vivo* PK of celecoxib released from LiQuidPolymers depot in comparison to bolus injection.



Polymer architecture

InnoCore's LiQuidPolymer is based on bioresorbable triblock copolymers composed of polyethylene glycol (PEG) and polyester blocks endcapped with aliphatic moieties. The polyester segments are composed of well-known monomers such as lactide, ε-caprolactone, glycolide and dioxanone – FIG 4. Due to their specific compositions and low molecular weight, LiQuidPolymers are liquid at room temperature. By varying the type and ratio of the monomers in the polyester block as well as the length of the aliphatic endcap a diverse family of customized polymers is available to create LiQuid-Polymer formulations with the desired release kinetics and polymer erosion rate.

Figure 5
Illustration and molecular structure of a LiQuidPolymer triblock copolymer



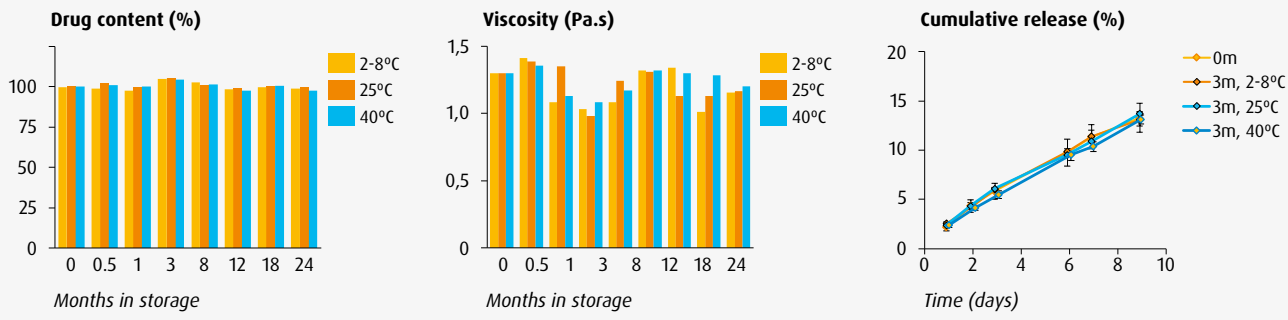
Bioresorption and biocompatibility

Under physiological conditions, LiQuidPolymer degrade via hydrolysis into non-toxic and biologically safe degradation products that are metabolized and/or excreted through the urinary pathway. LiQuidPolymers degrade gradually and completely, thereby avoiding polymer accumulation upon repeated administration or dose-dumping of degradation products. *In vivo* biocompatibility of LiQuidPolymer formulations has been assessed in many different animal models (mice, rats, rabbits, horses), showing no signs of local intolerance. Finally, in contrast to other liquid dosage forms, LiQuidPolymers form a soft but firm depot when administered, which can be removed if needed.

Scale-up and manufacturing

LiQuidPolymer formulations are preferably administered via prefilled syringes. Manufacturing of finished dosage forms only requires dissolving of the drug in the liquid polymer at room temperature using standard pharmaceutical mixing procedures and equipment, followed by liquid filling of the syringes and terminal sterilization. InnoCore offers fully integrated pharmaceutical development services for LiQuidPolymer formulations. Development is performed in InnoCore's research facilities in Groningen, the Netherlands, with cleanrooms for small-scale manufacturing of drug products suitable for pre-clinical evaluation and GMP certified analytical labs for quality control. LiQuid polymers are manufactured at kilogram scale by a reputable, GMP certified, CMO under a supply agreement. Through a network of qualified CMO's, InnoCore offers cGMP manufacturing of clinical supplies of LiQuidPolymer-based dosage forms.

Figure 6
LiQuidPolymer-based dosage forms can be stored at room temperature. Drug content, viscosity and (initial) cumulative release kinetics of LiQuidPolymer-based dosage forms after storage under refrigerated, ambient and accelerated conditions.



Partnering opportunities around SynBiosys

InnoCore is actively pursuing new partnerships to develop long-acting injectables based on its various biodegradable polymer-based drug delivery platforms, which include SynBiosys(R) microspheres, SynBiosys(R) implants and LiQuidPolymerTM. Being a medium-sized organization, we are flexible in constructing licensing and (co-)development partnerships around promising drug candidates. Our target-driven and cost-efficient organization is committed to Delivering Tomorrow's Medicines™ that offer added value to our partners and improve patients' quality of life. Flexibility, with the highest international quality standards, and a genuine belief in the value of collaborative partnerships are the key elements of the InnoCore approach. Please get in touch with us to discuss your ideas or partnering opportunities.

InnoCore Pharmaceuticals is based in Groningen. The city of Groningen is located in the northern part of The Netherlands.

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