



SynBiosys[®]

A biodegradable polymer-based long-acting injectable drug delivery platform for small molecules and biologicals

Brochure

Key attributes:

- + Precisely controlled release kinetics
- + Suitable for biologics and small molecules
- + Well preserved compound integrity and activity
- + Biocompatible and fully bioresorbable
- + Extensive safety dossier
- + Clinically validated
- + Strong patent protection

SynBiosys is an advanced biodegradable polymeric drug delivery system for the sustained release of small molecules and biologics. SynBiosys offers unsurpassed control over drug release kinetics and assures preservation of the bioactivity of sensitive therapeutic agents, thereby improving pharmacotherapeutic efficacy and reducing side effects. The platform is perfectly suited for the development of long-acting injectable dosage forms for the treatment of chronic and site-specific diseases. SynBiosys also offers excellent opportunities to upgrade current products and extend patent protection for effective life cycle management.

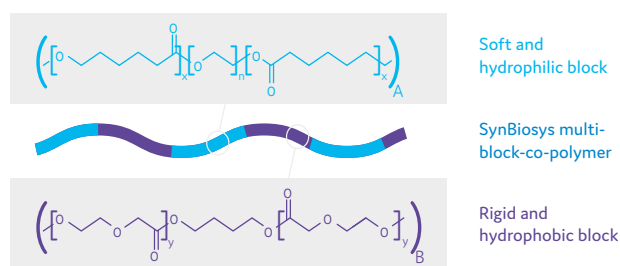


Figure 1
Example of a SynBiosys multi-block co-polymer.

Unique polymer architecture

The SynBiosys polymer platform comprises poly(ether ester) multi-block copolymers composed of building blocks based on different amounts and combinations of well-known monomers such as DL-lactide, glycolide, ε-caprolactone, p-dioxanone, and polyethylene glycol (Fig. 1). A major advantage of this system is the tunability of the chemical composition, creating a diverse family of customized polymers with tightly controlled properties (e.g. glass transition temperature, swelling degree, erosion rate).

SynBiosys polymers can be processed into various dosage forms, thereby allowing them to be used in a wide range of applications.

Dosage forms

SynBiosys polymers allow the development of long-acting-injectable (LAI) dosage forms in the form of microsphere suspensions, hot-melt extruded solid implants, and *in situ*-forming implants (Fig. 2) for basically any class of drug molecule. InnoCore has the disposal of advanced and proprietary manufacturing technologies, including a membrane emulsification solvent extraction-based micro-encapsulation process and low temperature hot melt (co)extrusion for implant production.

Figure 2
Examples of SynBiosys-based dosage: microspheres, extruded implants and *in situ* forming implants



| Disease area | Active compound | Route of administration |
|--------------------------|-----------------------|-------------------------|
| Osteoarthritis | Oncolytics | |
| Pain management | Hormones | Subcutaneous |
| Ocular diseases | Peptides | Intramuscular |
| Oncology | Growth factors | Intra-articular |
| Neurodegenerativ | Cytokines | Intravitreous |
| CNS (e.g. schizophrenia) | Recombinant proteins | Intrathecal |
| Contraception | Monoclonal antibodies | Intratumor |
| Metabolic diseases | Antibody fragments | |

Table 1
Examples of disease areas, compounds and routes of administration of SynBiosys long-acting injectables.

Unsurpassed ability to control the release kinetics

Lipophilic small molecules, peptides, and biologics have been successfully formulated into SynBiosys-based LAI dosage forms with precisely controlled release kinetics. Drug release from hydrophilic SynBiosys occurs through a combined diffusion/degradation mechanism. Via a selection and optimization of polymer composition, depot formulations with customized release kinetics (linear, pulsed, delayed-release) and release duration varying from a week to a year can be developed (Fig.3).

SynBiosys is designed to offer optimal control over release kinetics and bioactivity of therapeutic agents, improving pharmacotherapeutic efficacy and reducing side effects.

Hydrophilic polymers preserve integrity and activity of sensitive encapsulated compounds

One of the most critical aspects in the development of long-acting injectables for biologics is the preservation of the integrity and activity of the encapsulated compound. Due to its hydrophilic nature, SynBiosys forms a protein-friendly hydrogel-like matrix in which acidic degradation products do not accumulate. Avoiding the formation of an acidic microenvironment (as occurs in PLGA based LAI dosage forms) is crucial to assure the stability of pH-sensitive molecules, especially biologics such as recombinant proteins and monoclonal antibodies (mAb). The ability of SynBiosys to preserve the integrity and biological activity during product manufacturing and during release from the dosage form has been demonstrated both *in vitro* (Fig. 4) and *in vivo* (Fig. 5) for various biologics.

SynBiosys polymers degrade gradually and completely

Under physiological conditions, SynBiosys polymers degrade via hydrolysis into non-toxic and biologically safe degradation products that are metabolized and / or excreted through the urinary pathway. After completion of drug release, polymers degrade gradually and completely, thereby avoiding polymer accumulation upon repeated administration or dose-dumping of acidic degradation products, which minimizes the chance of long-term foreign body reactions.

Safe and clinically validated platform

In addition to extensive *in vitro* toxicity testing and assessment of *in vivo* biocompatibility in many different animal models (rats, rabbits, pigs, horses, monkeys), SynBiosys has been safely used in thousands of patients. An extensive biological safety report is available. Regulatory approvals have been granted for SynBiosys-based cardiovascular drug-eluting stents (COMBO Plus Dual Therapy DES, OrbusNeich®) in Europe, Japan and China since 2013.

Manufacturing of SynBiosys® dosage forms

InnoCore offers fully integrated pharmaceutical development services for microspheres, hot-melt extruded implants, and *in situ* forming implants. 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. Through a network of qualified CMO's, InnoCore also offers GMP manufacturing of clinical supplies of SynBiosys based dosage forms. polymers are manufactured under a supply agreement at kilogram scale under GMP.

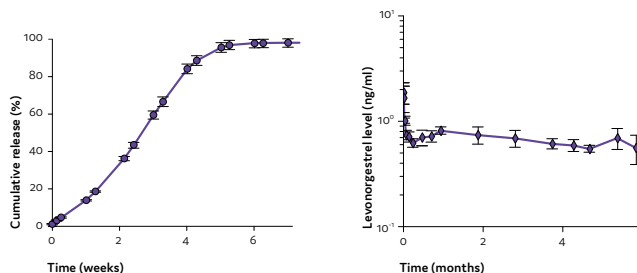


Figure 3

SynBiosys polymers allow the development of LAI dosage forms with precisely controlled release kinetics of small molecules and biologics.

Left: Cumulative *in vitro* release of human chorionic gonadotropin from SynBiosys microspheres.

Right: *In vivo* pharmacokinetics of a SynBiosys-based hot-melt extruded levonorgestrel implant.

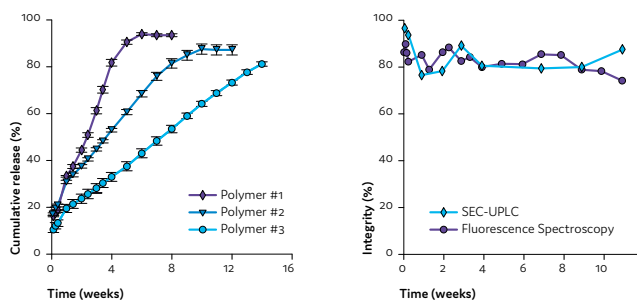


Figure 4

Hydrophilic polymers are compatible with large biologics, such as monoclonal antibodies (mAbs).

Left: Using different SynBiosys® polymers the release of mAb's can be controlled for up to several months.

Right: Antibodies remain structurally intact and properly folded during micro-encapsulation and throughout long-term release from the microspheres.

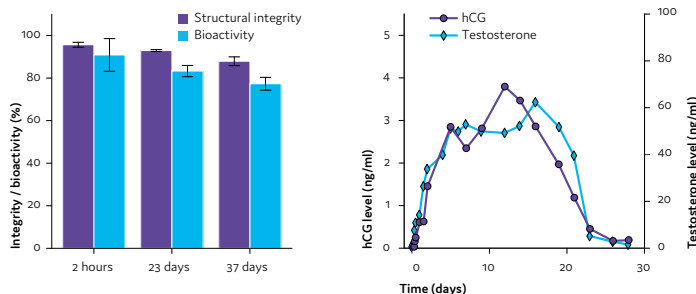


Figure 5

SynBiosys is designed to protect sensitive biologics and has shown to release biologics structurally intact and bioactive, both *in vitro* and *in vivo*. For more information see our Androsphere™ Application Note.

Left: Structural integrity (measured using SEC-UPLC) and bioactivity (measured using cell-based assay) of human chorionic gonadotropin (hCG) released from hCG extended release microspheres.

Right: *In vivo* PK/PD of hCG extended release microspheres following single subcutaneous injection. Biological activity of *in vivo* released hCG was confirmed by increased testosterone production as a result of elevated hCG plasma levels.

Partnering opportunities around SynBiosys

InnoCore is actively pursuing new partnerships to develop long-acting injectables based on its SynBiosys drug delivery platform. 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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