Sustained release formulations for biologicals:

from polymer design to cGMP production for clinical studies

Well-controlled drug release

- Sustained release of any biological
- Low burst with release of up to 6 months
- Protein integrity and bioactivity preserved

Safety and biocompatibility

- Excellent in vivo biocompatibility
- Complete in vivo degradation and safe degradation products
- Extensive biocompatibility/toxicity data packages
- Clinically validated polymer platform

Strong patent protection

- Matter of composition patents
- Effective patent protection > 2038

Uniformly-sized microparticles for parenteral delivery

- Absolute control over particle size (5–100 µm)
- Patient-friendly injectability
- High API doses of up to 100 mg/ml
- Reduced immunogenicity due to absence of undersized particles

Robust and scalable manufacturing

- Excellent lot-to-lot consistency
- Compatible with continuous manufacturing
- No need for sieving
- Compatible with aseptic production

Other formulation types

- Implants, films, wavers, coatings
- Nanoparticles

SAFC®

Pharma & Biopharma Raw Material Solutions

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64293 Darmstadt, Germany

MerckMillipore.com

support when you need it

With our experienced team of pharmaceutical experts and using our unique SynBiosys® drug delivery platform we can develop injectable sustained release delivery products for your peptide or protein-based therapeutics.

To find out more about this safe and versatile delivery platform for biologics; start a feasibility study; or discuss licensing and development opportunities, simply contact your Merck sales representative.

To discuss partnering opportunities or licensing and development opportunities, please visit **MerckMillipore.com/contactPS**

The typical technical data above serve to generally characterize the product. These values are not meant as specifications and they do not have binding character. The product specification is available through direct contact with us.

We provide information and advice to our customers on application technologies and regulatory matters to the best of our knowledge and ability, but without obligation or liability. Existing laws and regulations are to be observed in all cases by our customers. This also applies in respect to any rights of third parties. Our information and advice do not relieve our customers of their own responsibility for checking the suitability of our products for the envisaged purpose.

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Merck

BIODEGRADABLE POLYMER PLATFORM FOR BIOLOGICAL APIS

Sustained release of biologicals

The life science business of Merck operates as MilliporeSigma in the U.S. and Canada.

SAFC®

Pharma & Biopharma Raw Material Solutions

Large Peptides and Proteins

The challenge of developing sustained release biological formulations

Biodegradable polymers have for decades demonstrated their suitability in the drug delivery field. Sustained release formulations can minimize the side effects of drugs and at the same time improve their bioavailability. Moreover, sustained release formulations can help to improve patient compliance. Poor patient compliance is reported to cost the US healthcare system between 100 and 300 billion dollars a year.

However, traditional biodegradable polymers, such as PLGA and PLA, are not suitable for the sustained release of biologicals such as large peptides and proteins due to the following:

- Proteins may adsorb to the hydrophobic surface of PL(G)A polymers.
- The rigid polymer matrix of PL(G)A polymers does not allow protein diffusion, resulting in irregular polymer degradation-controlled protein release kinetics.
- Acidic polymer degradation products accumulate in the rigid PL(G)A matrix leading to an acidic micro-environment (in situ pH as low as pH 2).
- Acylation: nucleophilic primary amines can interact with the carboxylic acid end-groups of PL(G)A or its degradation products.

These factors can lead to the loss of biological activity; the reduction of the therapeutic efficacy; shorter shelf life and can potentially trigger an undesired immune response.

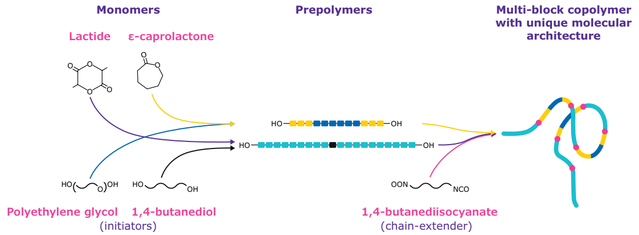
SynBiosys® Polymer Platform

Our solution for sustained release of biologicals

The SynBiosys® platform provides a suitable hydrophilic micro-environment to maintain protein integrity and activity during microencapsulation and sustained release.

This platform combines well-known, clinically proven and safe monomers to build customized, fit for-purpose multi-block polymers for delivery of any biological.

SynBiosys® multi-block co-polymers feature phase-separated morphology, combining hydrophilic amorphous and hydrophobic crystalline domains. The hydrophilic domains absorb water and swell to form a hydrogel-like structure that allow diffusion-controlled drug release. The crystalline domains act as physical cross-links providing structural integrity and controlling the degree of swelling.



Degradation of the SynBiosys® multi-block copolymer matrix occurs via hydrolysis, as in traditional PL(G)A formulations, followed by erosion. The final degradation products are safe and they are excreted through the urinary tract. The SynBiosys® platform has an extensive ISO-10993 biocompatibility/toxicity supporting data package. In vivo biocompatibility and degradation has been tested for a variety of formulation types (implants, microspheres, coated implants); routes of administration (subcutaneous, intramuscular, intra-articular, intravitreal, intrarenal) and species (mice, rats, rabbits, mini-pigs, pigs, horses, primates). Additionally, the Combo sirolimus eluting Dual Therapy coronary stent, with a SynBiosys®-based sirolimus eluting coating has been marketed since 2013.

Polymer degradation products and their route of excretion

Monomer	Degr. Product:	Excreted as:	Excretion Route:
Lactic acid	Pyruvic acid	CO_2 + H_2O	Urine, breathe
Glycolic acid			
ε-Caprolactone	ω-hydroxy heaxanoic acid	ω-hydroxy heaxanoic acid	Urine
PEG	PEG	PEG	Urine
Butanediisocyanate	Butanediamine (putrescine)	Butanediamine (putrescine)	Urine, breathe
Butanediol	Butanediol	Butanediol	Urine

Clinically Validated

Sustained release of intact and bioactive peptides and proteins

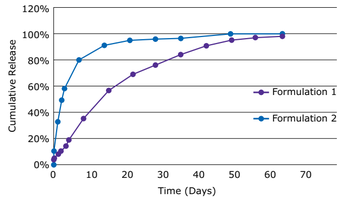
The versatile SynBiosys® platform allows easy optimization of critical quality attributes by modifying co-monomer type and weight fraction; block ratio; PEG molecular weight and content and polymer molecular weight. Customized multi-block co-polymers can be designed to meet the Target Product Profile (API dose, release kinetics, polymer erosion) of sustained release formulations of your biological.

Release controlled by block ratio of SynBiosys® multi-block copolymer

SynBiosys® polymers are phase separated poly(ether)ester-based multi-block copolymers consisting of hydrophilic and hydrophobic domains. Under physiological conditions, the hydrophilic domains absorb water leading to polymer swelling and formation of a hydrogel-like matrix from which encapsulated biologicals are released by simple diffusion. The release rate is controlled by the block ratio of the polymers. The hydrogel-like matrix also prevents accumulation of acidic degradation products and the occurrence of an in situ pH drop due to which the integrity and bioactivity of encapsulated biologicals is maintained.

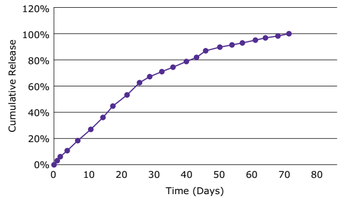
Insulin-like growth factor-1 (IGF-1)

- MW 7,655 Da
- 5 wt.% IGF (500 µg/10mg MSP)



Hepatocyte growth factor (HGF)

- MW 69,000 Da
- 2 wt.% HGF (200 µg HGF/10mg MSP)



Bioactivity of IGF-I released from SynBiosys® microparticles is preserved

Cell based bioactivity assay

The bioactivity of IGF-I released in vitro from IGF-1 loaded SynBiosys® microparticles up to 3 weeks was tested by an in vitro cell based assay (A431 cells) based on the activation of IGF-1 signal transduction pathway (Akt phosphorylation) and binding to its surface cellular receptor. Cell extracts were run in a SDS-PAGE gel and the amount of phospho-Akt was analyzed by Western Blot.

Released IGF-1 was intact and bioactive

Released IGF-I was functional and able to induce Akt activation during the complete duration of release, indicating that the integrity and activity of IGF-1 is preserved during the microencapsulation process and during its presence in the SynBiosys® polymer matrix up to completion of release.

Western Blot of AKT phosphorylation after activation of A431 cells with IGF-1 released at different time points from SynBiosys® microparticles.