FACTSHEET

PolyActive™

A biodegradable polymer-based drug delivery system

OctoPlus

PolyActive

PolyActive is a biodegradable polymeric drug delivery system. Its biodegradability, extensive safety record and linear release properties make PolyActive an excellent technology for the controlled release of proteins and lipophilic small molecules.
Products based on PolyActive can be used for both local and systemic administration, and have applications in pharmaceutics and medical technology.

PolyActive composition

PolyActive represents a series of poly(ether ester) multiblock copolymers, based on poly(ethylene glycol), PEG, and poly(butylene terephthalate), PBT (Figure 1). A major advantage of this system is the ability to vary the amount and length of each of the two building blocks, creating a diverse family of customized polymers. Polymer matrix characteristics such as rate of controlled release, degradation, swelling and strength can be precisely controlled by the appropriate combination of the two copolymer segments.

Degradation of PolyActive

PolyActive degradation occurs by hydrolysis of ester bonds and oxidation of ether bonds. The rate of degradation depends on the selected polymer composition: polymers with higher PEG content show a faster degradation profile. In addition, the configuration of the PolyActive product also impacts the degradation rate; e.g. microspheres, in general, degrade faster than dense cylinders (Table 1).

Key attributes of the PolyActive drug delivery system:

- + Suitable to encapsulate both small- and macromolecules
- + Controllable, including linear, release profiles
- + Low initial release: no burst
- + Strong in vitro – in vivo correlation
- + Well-preserved compound stability and activity
- + Biodegradable and biocompatible
- + Systemic and local applications
- + Extensive biological safety file
- + FDA approval and CE mark for medical devices
- + Patent protected

Table 1

Configuration	Example of delivery product	Example of active compound
Microspheres	Parenteral delivery systems	Biotherapeutics
Films	Topical delivery systems	Growth factors, anti-infectives
Gels/Wafers	Local drug delivery system	Oncolytics
Rods	Removable delivery systems	Psychotropics, contraceptives
Coatings	Implant coating delivery systems	Anti-proliferative agents

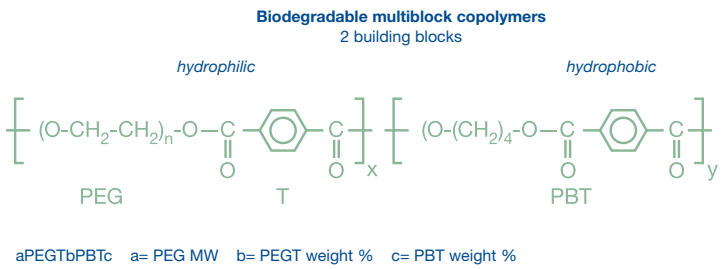
PolyActive applications

Using PolyActive allows the development of burst-free drug delivery systems, and its hydrophilic nature conserves the stability of labile biopharmaceuticals, such as proteins. Products made from PolyActive can be processed into various shapes and configurations, thereby allowing them to be used in a wide range of applications.

Performance

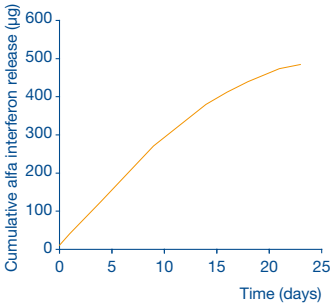
Release rates from PolyActive can be tightly controlled. Adjusting the copolymer composition gives control over both the diffusive and degradation properties of the polymer, allowing control over the release rates of diverse molecules.

Figure 1 PolyActive molecular structure



aPEGTbPBTc a= PEG MW b= PEGT weight % c= PBT weight %

Figure 2. Controlled release of alfa interferon from PolyActive microspheres.



In in vitro studies, a constant release of compounds has been achieved from PolyActive products without an initial burst effect, with release controllable from minutes to months (Figure 2).

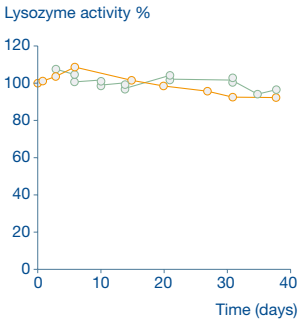
Excellent in vitro – in vivo correlation

PolyActive release profiles show an excellent congruence between release in vitro in PBS and in vivo in rats. With the use of PLGA-based microspheres, in vitro and in vivo release profiles may differ considerably. In contrast to PLGA-based microspheres, protein diffusion through the PolyActive hydrogel is the main rate-controlling factor, and this process progresses similarly in vitro and in vivo. This induces an excellent in vitro-in vivo correlation.

Preserved stability of the encapsulated compound

A key issue in the design of controlled release systems for biopharmaceuticals, and in particular proteins, is the integrity of the encapsulated compound. Due to the presence of hydrophilic poly(ethylene glycol) segments, PolyActive exhibits a hydrogel character, providing a natural environment for compounds such as proteins. Unlike PLGA, degradation products of PolyActive do not create an acidic environment. An acidic environment may cause the released protein to lose its activity. PolyActive preserves the activity and stability of the embedded compound. Assessment of the activity of a model protein (lysozyme) after release from PolyActive shows that the PolyActive matrix and production process have no adverse effects on protein activity (Figure 3). This is a considerable benefit compared to PLGA-based systems which have shown an extensive reduction of lysozyme activity. The preservation of biological activity after release from PolyActive has been demonstrated both in vitro and in vivo with other therapeutically relevant proteins and peptides (Table 2).

Figure 3. Activity of lysozyme released from two different PolyActive films. Molecular weight of the PEG segment is 1000 g/mole, and PEG/PBT ratio is 60/40 (I) and 40/60 (O).



PolyActive manufacturing

PolyActive microspheres, suitable for preclinical and clinical evaluation, can be produced under cGMP conditions in OctoPlus' pilot plant in Leiden, the Netherlands. PolyActive is manufactured under a supply agreement on 10-20 kilogram scale under GMP conditions. Polymers containing 30-90 weight percent soft segment and PEG-blocks with molecular weights varying from 300-10,000 g/mole are currently available.

Application of PolyActive in human pharmacotherapy

OctoPlus uses PolyActive to develop its controlled-release alfa interferon product Locteron™. Locteron combines PolyActive microspheres with BLX-883, a recombinant alfa interferon produced by OctoPlus' co-development partner Biolex Therapeutics in its patented LEX System℠. Figure 4 shows plasma levels of alfa interferon after subcutaneous injection of Locteron in humans. The graph shows that the release from the PolyActive microspheres does not induce a so-called burst effect and is gradual during approximately two weeks. For more information on Locteron, please refer to our Locteron Factsheet.

Similar results have been obtained with other pharmaceutical proteins in animal studies. Table 2 shows several compounds evaluated in combination with PolyActive

Safety and clinical data

In addition to over a decade of successful in vitro toxicity and biocompatibility assays, PolyActive has been used in implants in more than 5,000 patients and in over 2,000 animals (rats, rabbits, dogs, goats). An extensive biological safety report is available for the technology, and FDA and CE approval have been granted for two implantable orthopedic medical devices made from PolyActive.

Partner with OctoPlus for drug delivery with PolyActive

OctoPlus is actively pursuing new partnerships to develop products based on the PolyActive delivery system. As a medium sized organisation, we are flexible in constructing partnership agreements and open to take on some of the risk and cost for the development of promising compounds. Our priority is to build successful long-term drug delivery partnerships. Please feel free to contact us and discuss your ideas.

References

1 Bezemer J.M. et al.,
J. Controlled Rel., 64: 179-192, 2000

2 Bezemer J.M. et al.,
J. Controlled Rel., 67: 233-248, 2000

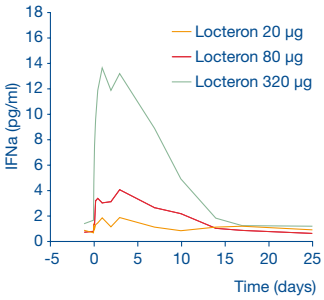
3 Bezemer J.M. et al.,
J. Controlled Rel., 67: 249-260, 2000

4 patent US5980948

Table 2: OctoPlus has evaluated different therapeutic peptides and proteins in combination with PolyActive.

Compounds	Size (kDa)	in vitro data available	in vivo data available
Salmon calcitonin	3.4	+	+
IFN alpha 2b	20	+	+
rhGH	21	+	+
TGF beta	25	+	+
RhEPO	35	+	+
rhBMP2	36	+	+
IgG antibody	160	+	-
Model proteins			
Lysozyme	14	+	+
Myoglobin	17	+	-
Carbonic anhydrase	29	+	-
BSA (albumin)	67	+	-

Figure 4. Pharmacokinetics of single dose Locteron



Person to contact
Gerben Moolhuizen,
Chief Business Officer

OctoPlus N.V.
Zernikedreef 12
2333 CL Leiden, the Netherlands
Telephone +31(0)71 524 40 44
Fax +31(0)71 524 40 43
E-mail octoplus@octoplus.nl
Website www.octoplus.nl

Person to contact in the USA
Michiel Lodder,
Director Business Development

OctoPlus Inc.
25 First Street, Suite 300
Cambridge, MA 02141, USA
Telephone +1 617 225 2510
Fax +1 617 225 2481
E-mail octoplus@octoplus-inc.com
Website www.octoplus-inc.com