ACTIfit®
STRONG, SAFE, SECURE

DEGRADATION

Degradation mechanism

Actifit® is made from a slowly degrading polymer with polycaprolactone and urethane segments. The degradation starts by hydrolysis of the ester bonds in the polycaprolactone segments (indicated by grey lines in ***Figure 1***). The urethane segments (indicated by black boxes in ***Figure 1***) are more stable than the polycaprolactone segments. They have a very slow degradation rate and will eventually be safely degraded by macrophages or giant cells, or become integrated into the surrounding tissue. This has been shown in biocompatibility studies using Actifit® and in a scientific study with a similar polyurethane.[1] The degradation is expected to occur over 4-6 years.[2]

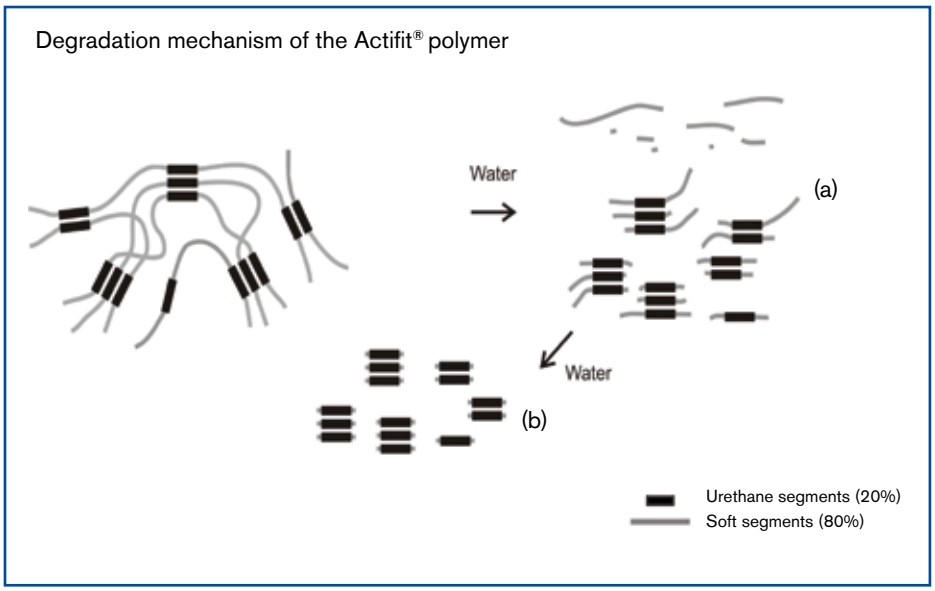

Figure 1.
Degradation mechanism of the Actifit® polymer.
(a) Hydrolysis of the ester bonds in the polycaprolactone segments.
(b) The urethane segments are more stable and have a very slow degradation rate. They will eventually be safely degraded by macrophages or giant cells, or become integrated into the surrounding tissue.

Degradation Testing

Orteq® has performed and passed the applicable standard ISO tests required for the approval of a class III medical device. The biocompatibility of the degradation products of the Actifit® polymer have been evaluated through the entire degradation process.

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1. Early Degradation Stage

a. Scaffold Debris

The knee is subject to high mechanical stresses, and it is possible that small particles may become loose from the scaffold. Orteq® carried out wear tests using the rabbit knee model to show safety of the scaffold particles, and the polymer passed this test.[3, 4]

b. Polymer Fragments

Following the degradation of polycaprolactone, only the urethane segments remain. The polymer has been designed so that these urethane segments are very small. As illustrated in ***Figure 2***, the urethane segments (~2-3 nm) are significantly smaller than a human macrophage (~20 µm). Therefore, these segments may be phagocytized without difficulties by the macrophages.

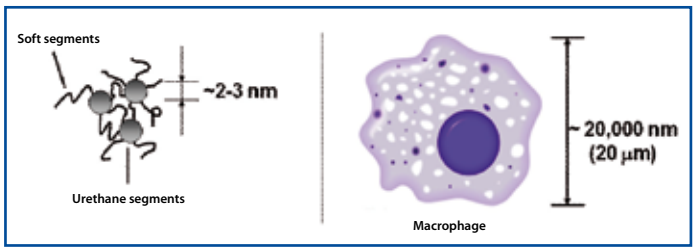

Figure 2.
Size comparison of the urethane segments (~2-3 nm) with a human macrophage (~20µm). A macrophage is about 6,000-10,000x larger than a urethane segment.

2. Intermediate Degradation Stage

Following the hydrolysis of the polycaprolactone segments, polycaprolactone oligomers (shorter chain segments) and urethane segments are observed during the next stage of the degradation process.

a. Polycaprolactone Oligomers

Since polycaprolactone is used in a wide range of medical devices, most notably sutures (Monocryl® by Ethicon, and Caprosyn® by Covidien) and suture coatings (Vicryl® and Panacryl® by Ethicon, and Dexon® and Polysorb® by Covidien), the safety of their intermediate degradation products is well understood and proven. These products are approved by the FDA and distributed globally.[5]

b. Urethane Segments

To assess the biocompatibility of the remaining urethane segments, a combined subchronic toxicity and local tolerance study of 13 weeks, and a chronic toxicity study and local tolerance study of 26 weeks were carried out. The urethane segments were proven to be safe, well-tolerated and taken up by macrophages.[3, 4]

3. Final Degradation Stage

The final degradation stage represents breakdown of the intermediate degradation products into their molecular components.

a. Hydroxyhexanoic acid (HHA)

HHA is the end degradation product of polycaprolactone, an FDA-approved and widely used polymer. The safety of HHA is well-established.[5]

b. 1,4-Butanediol (BDO) and 1,4-Butanediamine (BDA).

BDO and BDA are the end degradation products of the urethane segments. The maximum theoretical amounts of BDO and BDA that will be released from an Actifit™ scaffold are 60 and 90 mg, respectively. Moreover, due to the slow degradation of the urethane segments, BDO and BDA will be released in very low amounts over a very long time. BDO has undergone extensive testing and proven to be non-toxic even at high concentration levels.[6] BDA is also known as putrescin. Cells naturally synthesize small quantities of putrescin which is considered necessary for cell division. Putrescin does not pose a risk due to its short lifetime in the body and absence of toxicity at the levels released. The degradation end products will be cleared through diffusion or catabolism.[6]

References

1. van Minnen B, van Leeuwen MB, Kors G, Zuidema J, van Kooten TG, Bos RR. In vivo resorption of a biodegradable polyurethane foam based on 1,4-butanediisocyanate: A three-year subcutaneous implantation study. J Biomed Mater Res A. 2008; 85A: 972-982.
2. Lewandrowski KU, Wise DL, Yaszemski MJ, Gresser JD, Trantolo DJ, Altobelli DE (Eds.). Tissue Engineering and Biodegradable Equivalents, Scientific and Clinical Applications, CRC Press, 2002.
3. Data on File, R08006 In-vitro degradation study.
4. Data on File, R06036 Summary report Actifit™ biocompatibility testing.
5. FDA, Covidien, Ethicon.
6. Data on File, R05002 Toxicity.

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