

# DURIN™ Biodegradable Implants

The DURIN biodegradable implant technology is a platform for **parenteral delivery of drugs for periods of weeks to six months or more**. The technology is based on the use of biodegradable polyester excipients, which have a proven record of safety and effectiveness in approved drug delivery and medical device products.

## DURIN Implants have the Following Features:

<p><b>Superior delivery kinetics.</b></p>	<p><b>Flexibility.</b></p>	<p><b>Superior drug loading and stability.</b></p>
<p>Compared to microspheres or in situ gel forming depots, DURIN implants offer release kinetics that are closer to zero order, with essentially no initial burst following administration.</p>	<p>DURIN implants can deliver a wide variety of drugs including hydrophobic and hydrophilic compounds as well as small and large molecules. Our proprietary implant design allows for first order, zero-order, delayed or biphasic drug release profiles. Durations can range from weeks to six months or more.</p>	<p>DURIN implants can be manufactured with very high drug loading (up to 70-80%) making extremely small implants feasible. DURIN implants are ideal for long term delivery because, within the implant, drug exists in solid form which enhances drug stability.</p>
<p><b>Fully biodegradable.</b></p>	<p><b>History of safe human use.</b></p>	<p><b>Cost effective.</b></p>
<p>DURIN implants degrade by hydrolysis after drug release and are fully absorbed by body tissues. Hence, a surgical intervention to remove the device is not required.</p>	<p>DURIN implants are manufactured using lactide-glycolide co-polymers (biodegradable, biocompatible polymer excipients) that have a long history of safe human use in medical devices and drug implants.</p>	<p>Unlike microspheres and other implants, the DURIN technology is readily scaled to large production volumes in a cost effective manner.</p>



## Overview of the Technology

The DURIN biodegradable implant technology is based on the use of biodegradable polyesters as excipients for implantable drug formulations. This family of materials, which is used extensively in medical devices and drug delivery applications, includes the polymers and copolymers prepared from glycolide, DL-lactide, L-lactide, and  $\epsilon$ -caprolactone. These thermoplastic materials are stable when dry but degrade by simple hydrolysis of the polymer backbone when exposed to an aqueous environment. The degradation times and physical properties of the biodegradable excipient can be engineered to achieve a wide variety of drug delivery goals by adjusting monomer composition and distribution, polymer molecular weight, and endgroup chemistry.

In addition to polymer engineering, the physical structure of DURIN implants is designed to achieve the desired therapeutic outcome. The overall form of the implant is typically a small rod or pellet that can be placed by means of a needle or trochar. The composition of the rod or pellet can be monolithic, where the drug is uniformly dispersed throughout the excipient. Alternatively, reservoir-type designs are also possible in which the rod or pellet is composed of a drug-rich core surrounded by a rate-controlling membrane. Depending on drug chemistry and desired kinetics, the membrane may or may not contain drug. Typically, the drug and excipient are mixed together, and the mixture is formed into a fiber, rod, tablet, or pellet by an extrusion or molding process. The rate-controlling membrane, if required, may be applied during or subsequent to the core-forming process.



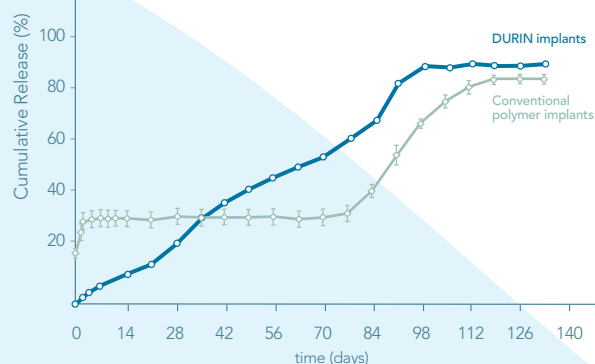
DURIN implants can be formulated with drug loading as high as 80 wt %. Thus, very small implants are able to provide prolonged therapy.

The release of the drug from the implant can occur by degradation of the excipient, diffusion of the drug through the excipient or pores in the excipient, or a combination of degradation and diffusion. The relative contributions of these processes and the overall release profile are controlled by a number of variables including drug content, excipient composition, and implant design. As a result, a variety of drug delivery profiles including first-order, zero-order, delayed, and biphasic drug release can all be achieved with the DURIN implant technology.

## Peptides

Peptides are not typically permeable through dense biodegradable polymeric membranes, hence they are difficult to deliver with polymer implants. We have done a great deal of work with LHRH analogs such as leuprolide and goserelin, and have found that excipient properties can be modified so that these larger, water-soluble compounds can be delivered in a near zero-order manner. The figure below shows the release of a peptide from DURIN biodegradable implants compared to conventionally designed hydrophobic DL-PLG implants. The DURIN implant demonstrates near zero-order release with no initial burst. These implants were later used in Phase I human clinical trials.

In vitro release of a peptide from monolithic implants manufactured for clinical trials

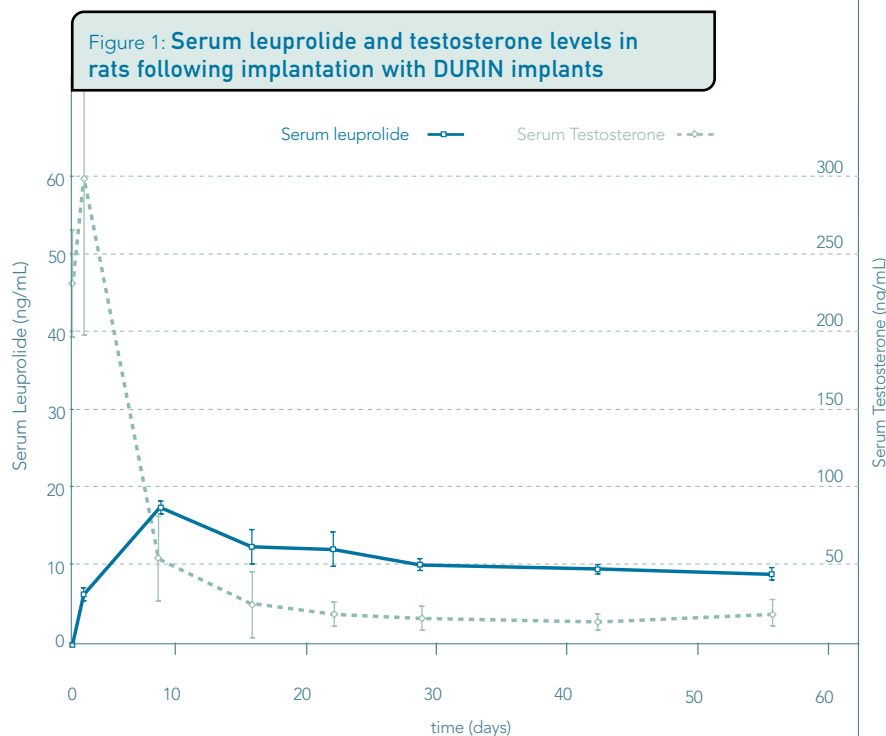


## Safety and Toxicology

The biodegradable polyester excipients used in DURIN implants have been approved in over 30 medical devices and drug delivery systems since the first suture based on poly-glycolide was approved by the FDA in the 1970's. One notable example of a commercially-successful biodegradable implant formulation is Zoladex<sup>®</sup>, which delivers goserelin acetate for the treatment of prostate cancer. These excipients and the products based on them have a long history of use and acceptance by the FDA and other regulatory agencies.

## Compounds Delivered Using DURIN Technology

The DURIN technology has successfully achieved controlled, zero-order drug release for up to 6 months *in vivo*. Because of the broad range of physical properties and degradation times that can be designed into biodegradable polyesters, DURIN implants can deliver a wide variety of drugs including both hydrophobic and hydrophilic compounds as well as small and large molecules. Peptides are particularly suitable for incorporation into the DURIN implant technology. Drug loading as high as 80 wt % has been achieved, but generally range from less than 1 wt % to 60 wt %. Thus, an implant 2.5 mm in diameter and 3 cm in length can provide a dose of up to 100-150 mg of active ingredient.

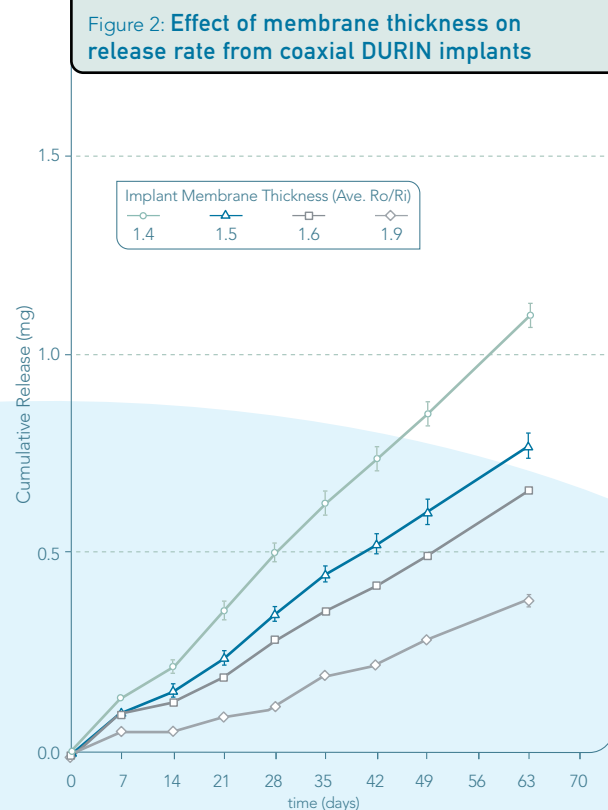


## Drug Delivery Performance

Figure 1 shows near zero-order release of an LHRH analog from a DURIN biodegradable implant and the corresponding effect on testosterone levels in male rats. In this example, the DURIN implant was of a monolithic design in which the physical properties and degradation rate of the implant were engineered to provide uniform delivery of the analog for 2 months with little or no burst following implantation.

Implants can also be designed with permeable biodegradable membranes that achieve approximate zero-order delivery of drug. Figure 2 illustrates how membrane thickness can be used to control the release of naltrexone, a narcotic antagonist, from a reservoir type DURIN implant.

Similar results can be achieved by using microporous biodegradable membranes to control the release of drugs that are highly water soluble or osmotically active. For example, we have successfully developed implants in which the membrane includes a pore forming agent that will leach out upon exposure to an aqueous environment, creating a microporous membrane.



## DURIN Manufacturing

Typically, we use melt extrusion at modest temperatures to produce biodegradable implants for drug delivery. The active and excipient are combined and fed to a melt extruder to produce a bulk rod, which is then cut to produce the unit dose. For co-axial, membrane-controlled implants, two extruders are operated to simultaneously produce the core and membrane in a continuous process. For particularly heat labile compounds, the DURIN technology is also compatible with proprietary manufacturing methods other than extrusion that ensure drug stability. Because DURIN implants are produced using continuous manufacturing processes, batch size is determined by the length of the extrusion run. We have successfully prepared several clinical batches of biodegradable implants at a batch size of more than 2000 doses.

## Contact

In collaboration with various pharmaceutical and biotechnology partners, DURECT ([www.durect.com](http://www.durect.com)) develops innovative controlled-release drug products based on our leading drug delivery technologies. To put our technology, experience and expertise to work for you, contact us today:

Nigel Ray  
Senior Director of New Ventures and Business Development  
DURECT Corporation  
10240 Bubb Road  
Cupertino, CA 95014  
Ph: 408-346-1053  
Fax: 408-777-3577  
[nigel.ray@durect.com](mailto:nigel.ray@durect.com)

