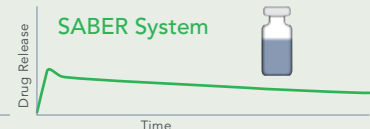
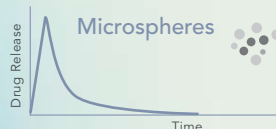


# SABER™ Delivery System

The SABER Delivery System is a parenteral delivery platform with strong patent protection that can **successfully deliver therapeutic levels of a wide spectrum of drugs from a few days to 3 months from a single injection.** The system offers significant advantages over competing systems in terms of product performance, ease of administration, and manufacturability.

## SABER has the following features:

<b>Peptide/Protein Delivery.</b>	<b>Less Burst.</b>	<b>High Drug Payload.</b>
<p>Because its hydrophobic nature tends to stabilize proteins and peptides, SABER is well suited for long-term delivery of these novel therapeutics.</p>	<p>Administration of a SABER depot is associated with less post-injection burst than is typical of polymer-based systems. <i>In vivo</i> delivery of a therapeutic protein from a SABER formulation was compared with that from a commercially available PLGA microsphere formulation. Ten-fold lower burst was observed with the SABER formulation.</p>	<p>Drug payload in a SABER formulation can be as high as 30%, allowing for higher doses and smaller injection volumes than are typical for polymer-based formulations.</p>
<b>Ease of Administration.</b>	<b>Strong Patent Protection.</b>	<b>Ease of Manufacture.</b>
<p>Small needle gauges, small injection volumes and low solution viscosity result in easier, less painful administration.</p>	<p>DURECT has a strong intellectual property position covering SABER, SABER-like materials, and various applications of this technology to pharmaceuticals and drug delivery.</p>	<p>Compared to microspheres and other polymer-based systems, SABER is readily manufacturable at low cost.</p>



## Overview of the Technology

The SABER Delivery System is an injectable, biodegradable delivery system technology consisting of sucrose acetate isobutyrate (SAIB), a pharmaceutically acceptable solvent, and one or more additives. SAIB is a very hydrophobic, fully esterified sucrose derivative with a nominal ratio of six isobutyrate to two acetates, that exists as a very viscous liquid. The drug to be delivered by the SABER system is dissolved or dispersed in the SAIB/solvent solution for subsequent injection subcutaneously or intramuscularly. Upon injection, the SABER system forms a high viscosity depot from which the drug is slowly delivered.

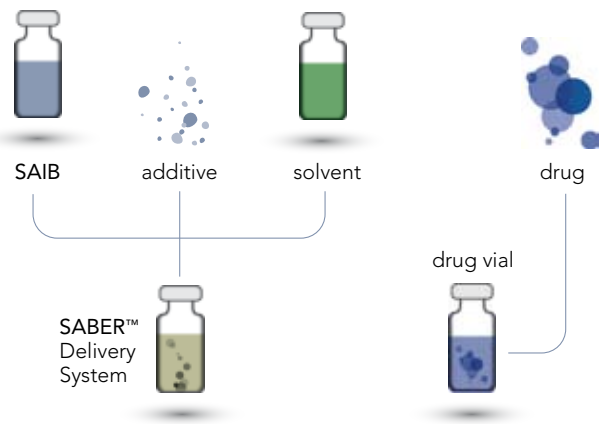
### The SABER Drug Delivery Technology



Time lapse sequence of an in vitro assay showing different rates of delivery from 3 SABER formulations.

The final high viscosity SABER depot is adhesive, bio-compatible and biodegradable and is suitable for both systemic and local drug administration. Sustained and controlled drug release can be tailored for a period from a few days to 3 months or more. The amount and duration of drug release from SABER can be controlled through a number of formulation variables such as drug loading, type and amount of solvent, and type and amount of additive, if any. For example, if SABER is formulated with a water-soluble solvent such as ethanol, the solvent will diffuse rapidly out of the injected volume leaving a high viscosity depot that is well suited for long-term drug delivery of small molecules. The use of a more hydrophobic solvent, such as benzyl benzoate, results in a less viscous depot that is better suited to delivery of large molecules that diffuse less rapidly.

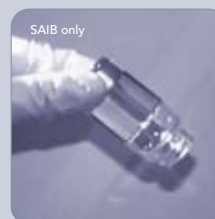
### The SABER System



Upon injection, the SABER System forms a high viscosity depot from which drug is slowly released.

The SABER Delivery System has advantages over polymer-based systems in terms of lower solution viscosity prior to injection, relatively low solvent content and higher drug loading. This translates into easier injectability, with lower injection volumes, smaller needle sizes and better patient acceptance.

With the addition of small amounts of solvent, the viscosity of SAIB is reduced by several orders of magnitude. For example, the addition of 15% ethanol reduces the viscosity of SAIB from more than 1.2 million cP to less than 100 cP as seen below.



Addition of a small amount of solvent results in a large reduction in the viscosity of SAIB

# Compounds delivered using SABER Technology

The SABER technology has successfully achieved durations of drug release of up to 3 months *in vivo*. Some of the attractive features of the system include drug release with little burst, ease of manufacture, ease of administration, and high drug payload, in a system with strong patent protection.

There are no inherent limitations on the types of drugs that can be delivered parenterally using the SABER technology. Delivery of a large spectrum of drugs, from small molecules to peptides and proteins has been successfully demonstrated.

DURECT Corporation has achieved drug loadings of as high as 30% in parenterally acceptable formulations. The table below compares typical injection volumes for SABER to polymer-based systems such as microspheres and implants. It can be seen that the same dosage can be achieved with SABER using smaller gauge needles and in many cases lower injection volumes than those possible with microspheres or implants.

DURECT has evaluated sustained release formulations of SABER with the following types of compounds:

- |                                                  |                   |
|--------------------------------------------------|-------------------|
| Steroids                                         | NSAIDs            |
| Peptides                                         | Local anesthetics |
| Proteins (including growth factors and hormones) | Analgesics        |
| Anti-tumor agents                                | Antiviral agents  |
| Antibiotics                                      | Antipsychotics    |
|                                                  | Anticoagulants    |

Parenteral Delivery Platform	Injection Size	Needle Size
<b>SABER</b>	<b>0.67 mL</b>	<b>25 gauge</b>
Microsphere	1.6 mL	23 gauge
Implant	2.3 x 80 mm	12 gauge

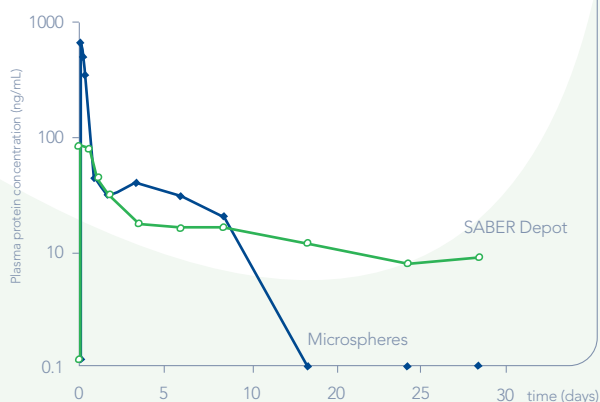
In this comparison, it was assumed that the formulations were for a 30-day system delivering 200 mg of drug or 6.67 mg/day with a loading of 60% for an implant and 50% for microspheres that are injected with 3 parts of diluent.

## Drug Delivery Performance

As shown in the graph below at left, SABER can deliver large molecules such as proteins with significantly lower burst and for longer durations than polymer-based delivery systems.

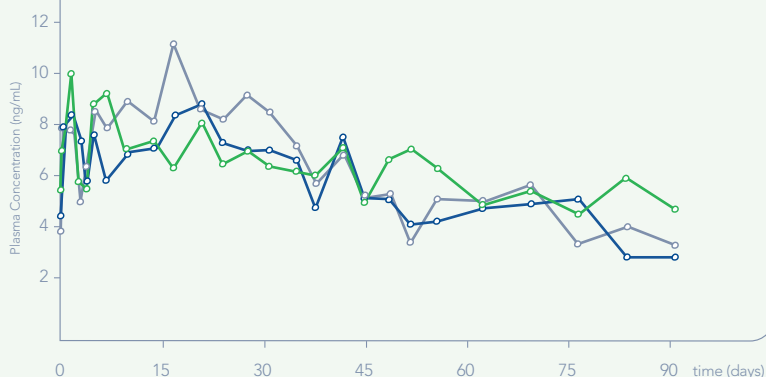
Representative data on delivery of small molecules from a SABER depot are shown in the graph below at right. Delivery can be accomplished with acceptable burst for durations of one to three months from a single depot injection. Delivery duration can be altered through solvent selection, by varying solvent loading or through the addition of rate-modifying excipients.

**A Comparison of the Release of a Proprietary Protein from an Injection of SABER and PGLA Microspheres**



SABER can deliver proteins *in vivo* with significantly lower burst and for longer duration than polymer-based microspheres

**The Release of a Proprietary Hydrophobic Drug from a SABER Injection**



An intramuscular injection of SABER in rabbits can deliver a proprietary small molecule drug for 90 days

## SABER Manufacturing

SABER-based products are manufactured in a simple liquid mix and fill process using conventional tanks and stirrers. DURECT's research and pilot plant facility in Cupertino, California include clean room and aseptic processing space capable of manufacturing and filling SABER products under GMP conditions. In our experience, the manufacturing of SABER-based products is readily scalable. The challenges for scale up of SABER products are typical of conventional parenteral products and are considerably less than those for polymer-based microsphere and depot products.

## Contact

In collaboration with various pharmaceutical and biotechnology partners, DURECT is developing 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:

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