Using Drug Nanoparticles To Modify the Release Kinetics of Ethylene Vinyl Acetate Long-Acting Implants

Harsh Patel[1], Jeffrey Haley[1], Edward Dobrzykowski[1], Gerald Ferrara[1], Nikolay Houbenov[2], Nnaemeka Ezeanowi[2], Aleksi Syrjä[2], Alexandre Ventura[2]

[1]Celanese Corporation, Irving, TX, USA
[2]Nanoform, Helsinki, Finland

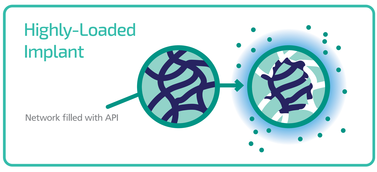
Overview

Ethylene Vinyl Acetate (EVA) implants are well-established for long-acting subcutaneous drug delivery, with multiple approved drug products. It is desirable to produce implants with as high of a drug loading as possible.

An associated challenge is that at high loadings, monolithic implants sometimes exhibit a high initial burst release and greater than desired overall release rate. The standard solution used by multiple marketed products is to produce multilayer implants via coextrusion. These consist of a highly loaded core with a rate-limiting outer layer – this layer reduces the burst release and can be used to tune drug release kinetics in a manner that is independent of drug loading in the core.

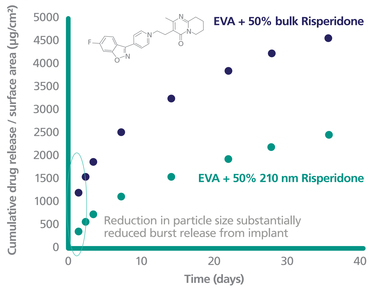
There are cases where designing a multilayer implant is inconvenient, however, so there is a drive to develop alternative methods to optimize drug release kinetics. For example, non-cylindrical implants often are best manufactured via injection molding, which would require additional manufacturing steps to apply a rate-limiting layer to an implant.

This study sought to clarify the effect of drug particle size on drug release kinetics from highly-loaded EVA implants, which was first reported more than 40 years ago,[1] but has not been broadly explored as a method to modulate drug release. In highly-loaded monolithic implants, drug release occurs through a network of pores created by dissolved drugs; changing particle size changes the architecture of this network, which is expected to alter drug release kinetics.



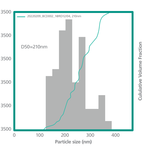
This study evaluates the effectiveness of using drug nanoparticles in EVA implants with two potent drugs: risperidone and fingolimod. Reducing drug particle size resulted in a slower overall drug release and reduced the initial burst release of risperidone.

In Vitro Release of Risperidone Implants



SEM

PSD

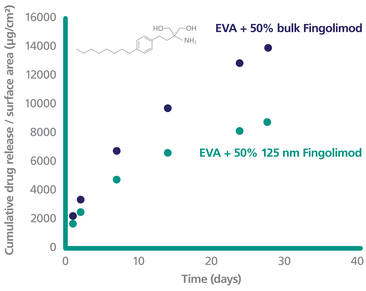


- Risperidone is an atypical antipsychotic that has been used in long-acting injectable drug formulations.
- Risperidone particles with a D50 = 210 nm were incorporated into EVA at 50% by weight via hot-melt extrusion.

Key takeaway

Implants produced with CESS® nanoparticles of risperidone exhibited much lower initial burst release and a slower overall release rate.

Accelerated In Vitro Release of Fingolimod Implants



- Fingolimod is an immunomodulating compound used in the treatment of multiple sclerosis. It is sufficiently potent for use in a long-acting drug delivery implant.
- Two batches of fingolimod nanoparticles were blended together to produce a sample with a nominal D50 = 125 nm. These particles were incorporated into EVA at 50% by weight via hot-melt extrusion.
- Due to the very low water-solubility of fingolimod, elution studies were conducted in an accelerating media (1:1 Ethanol:PBS).

Key takeaway

The implant containing CESS® nanoparticles exhibited a slower release rate when compared with micronized fingolimod.

Experimental Details

Hot-Melt Extrusion

For each of the batches produced, cryogenically ground Ateva® 2820A was blended with active pharmaceutical ingredient (API) in a 1:1 weight ratio to produce blends consisting of 50% API. Blends were then fed into the feed throat of an 11mm twin-screw extruder. For all extrusion runs the melt temperature was maintained between 90-95°C. Polymer is collected as strands and cut to produce implants. All weighing and extrusion steps were conducted in flexible isolators.

In Vitro Drug Release Methods

Six rods of each formulation were placed into individual glass vials containing 40 mL of elution media (see below*). At each timepoint, elution media was completely removed and replaced with fresh media. The concentration of API in the media for each timepoint was determined via HPLC. The total quantity of drug release is reported in units of mass normalized by the surface area of the implant sample.

*Risperidone media: phosphate buffer pH 7.0
*Fingolimod media: 1:1 ratio of PBS (pH=7.4):ethanol

CESS® Process

Nanoformed fingolimod and risperidone were produced via recrystallization of the API from supercritical CO_2 in the CESS® process. Pressure and temperature were set and controlled for maximum solubility and optimal nanoparticle formation during expansion. After sublimation of the CO_2, the nanoformed fingolimod and risperidone were characterized, showing a D50 of 60 nm and 200 nm, respectively.

Conclusions

CESS® produced nanoparticles of two potent drugs, risperidone and fingolimod, resulted in a slower release rate in EVA implants relative to bulk material

Nanoformed risperidone also exhibited a much lower initial burst release.

These results demonstrate the exciting potential of CESS® nanoparticle engineering as an alternative method to solve the long-standing challenge associated with the drug release kinetics of EVA implants for long-acting subcutaneous delivery.

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