Sustained Release of Biotherapeutics from a Solid Parenteral Dosage Form

Harsh Patel, PhD

Senior Scientist, Celanese Pharma & Medical

CRS Annual Meeting

July 11 - 15, 2022

Celanese

The chemistry inside innovation™

Celanese's Focus to Deliver Pharmaceutical Solutions:

Innovation through Implantable Drug Delivery

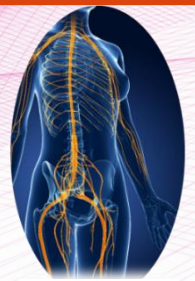
Addresses your most challenging drug delivery problems

Broad API compatibility

Women's Health

Oncology

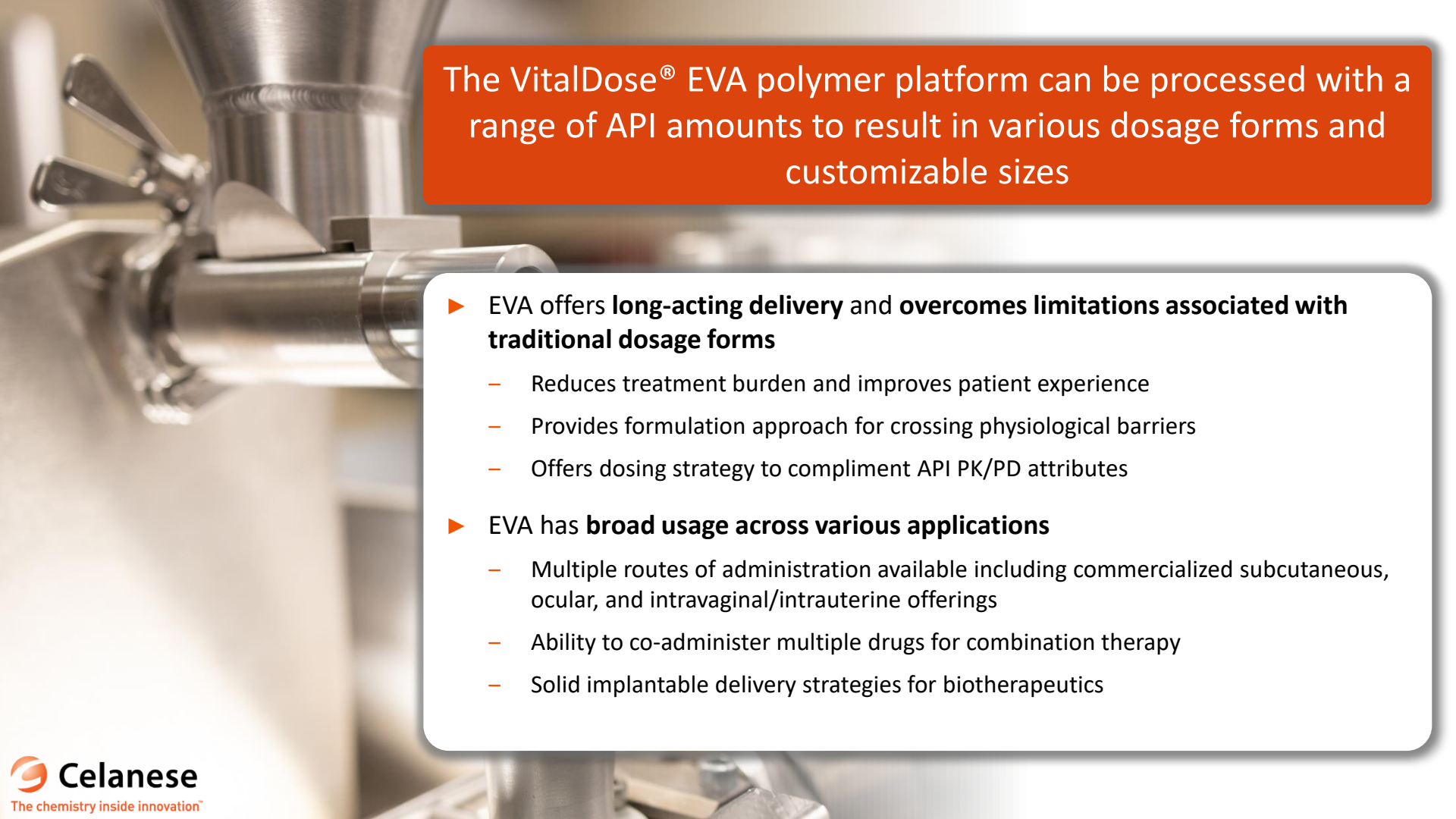
Ophthalmic Conditions



Other Therapeutic Areas

Versatile drug delivery solution

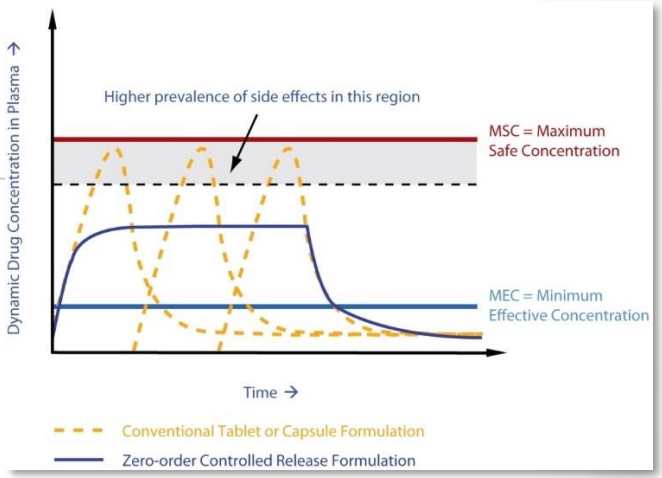
Feasibility support for innovative formulation development



The VitalDose® EVA polymer platform can be processed with a range of API amounts to result in various dosage forms and customizable sizes

- EVA offers **long-acting delivery** and **overcomes limitations associated with traditional dosage forms**
  - Reduces treatment burden and improves patient experience
  - Provides formulation approach for crossing physiological barriers
  - Offers dosing strategy to compliment API PK/PD attributes
- EVA has **broad usage across various applications**
  - Multiple routes of administration available including commercialized subcutaneous, ocular, and intravaginal/intrauterine offerings
  - Ability to co-administer multiple drugs for combination therapy
  - Solid implantable delivery strategies for biotherapeutics

VitalDose® EVA provides localized and systemic release of a wide range of molecules



Tunable and precise parenteral delivery offers a route to innovation by bypassing physiological barriers

Celanese
The chemistry inside innovation™

The Use of VitalDose® EVA Platform in Drug Delivery

Long History of Use in US & EMEA Approved Products

EVA has a long history of use in approved parenteral drug products in the US and EMEA

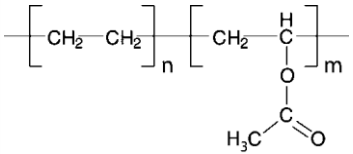
Ophthalmic Insert & Ocular Implant

Intravaginal Ring

Intrauterine Device

Subcutaneous Implant (rod)

Compatibility and processability



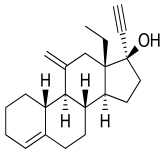
VitalDose® provides ease of use and versatility while Celanese's expertise provides knowledge around processing and prototyping

Celanese
The chemistry inside innovation™

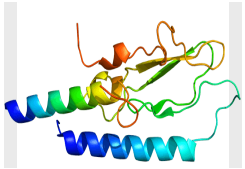
VitalDose® EVA provides ease in development across a broad range of API

Sustained Delivery of Small Molecules and Biopharmaceutics

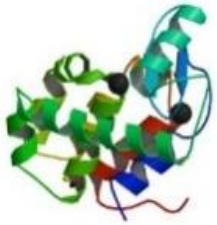
- Versatile dual formulation capability gives release for small API to large biotherapeutics drugs
- Adaptable designs provide tunable controlled release from months to years
- Provides simplicity in development compared to other polymer platforms
- VitalDose® EVA is commercially established for small molecules and is in development with partners for large biologics



Etonogestrel
0.325 kDa



GLP-1
3-4 kDa



Lysozyme
15 kDa

mAbs
100+ kDa

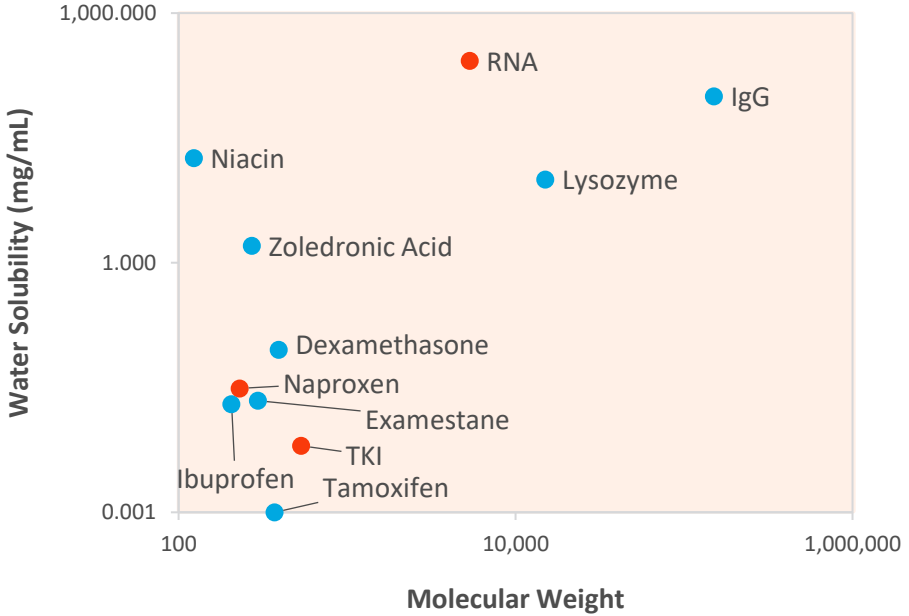
Diffusion ***RELEASE MECHANISM*** *Porous Network*

Celanese
The chemistry inside innovation™

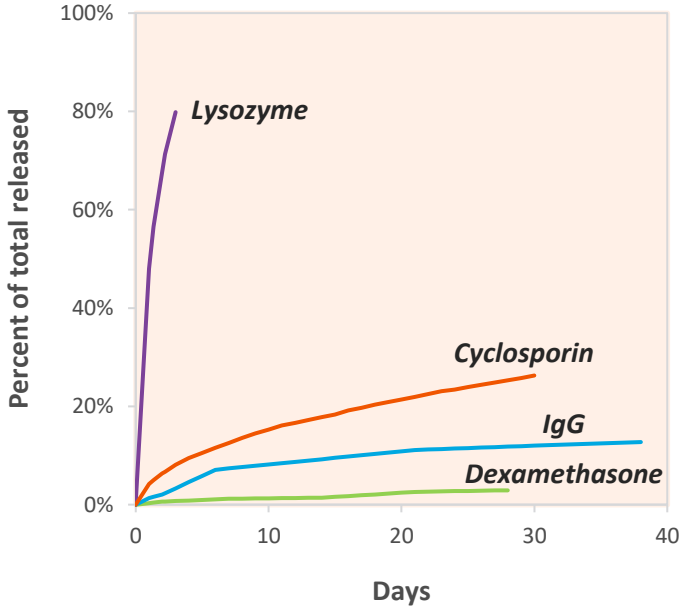
The VitalDose® EVA Platform has broad compatibility

APIs of all characteristics can be delivered via the platform

VitalDose® EVA can be formulated with APIs of varying molecular weights and solubilities



Varying release profiles can be achieved across molecules classes

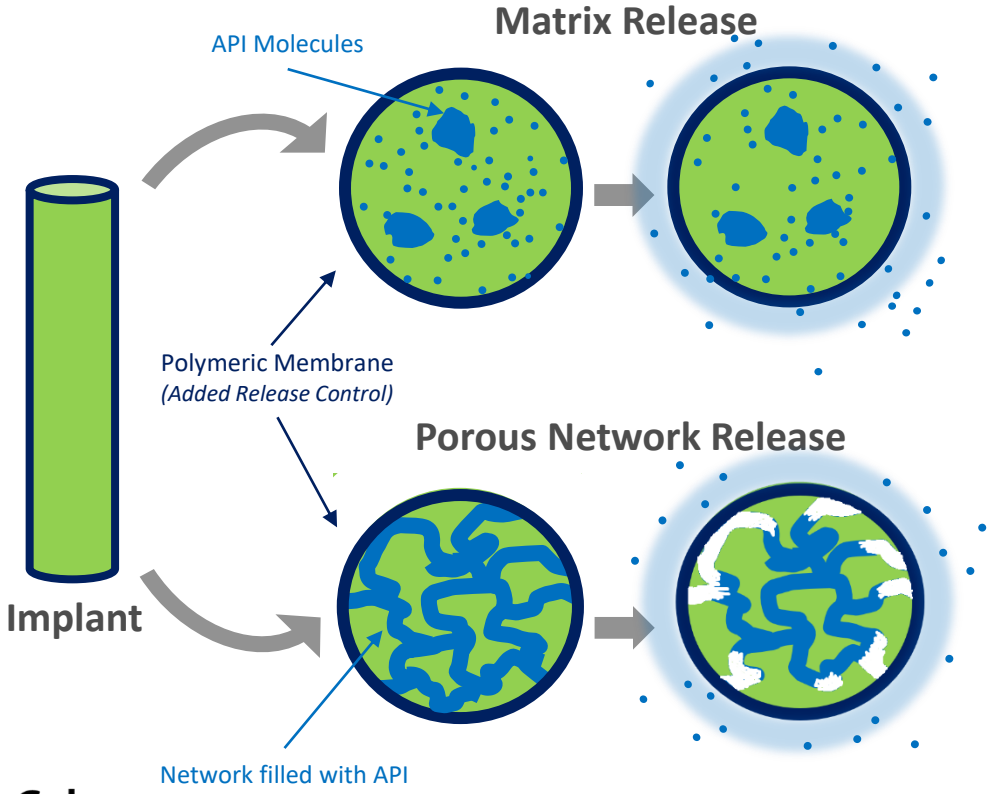


Proven In Progress *Additional molecules in progress*

Celanese
The chemistry inside innovation™

Addressing a Wide Range of Drugs and Release Needs:

The Broad Capabilities of the VitalDose® EVA Drug Delivery Platform



Dual formulation capabilities control drug elution through:

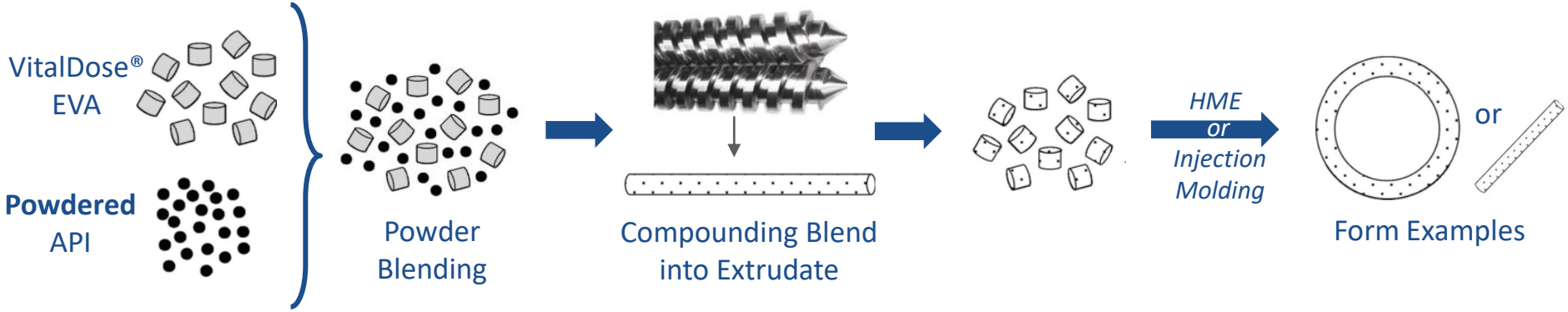
- Matrix (small molecules)
- Porous Network (large molecules)

- Sustained release from EVA is possible in multiple configurations
- Release rate can be tuned by adjusting loading

Celanese
The chemistry inside innovation™

The Ease of Processing with Powdered API

Working with Small and Large Therapeutics



- VitalDose® EVA is blended with powdered API
- **Low melt temperature options** offer optimal stability and compatibility

- Powdered API and EVA are **combined and compounded into extrudate**
- **Small quantities of API** can be used to generate small volume samples

- The extrudate is pelletized for use in **extrusion or injection molding**
- Processing flexibility results in a **versatile range of form factors**

Celanese
The chemistry inside innovation™

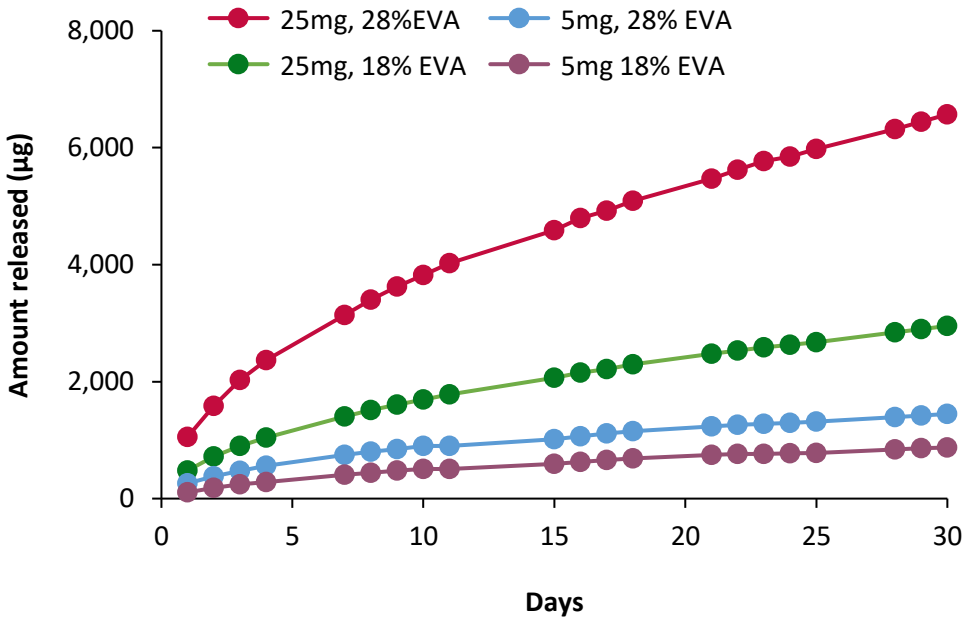
Images adapted from: Malcolm et al. *International Journal of Women's health (2012)*

Matrix Based Formulation

Long-acting, controlled release of small molecule achievable in VitalDose® EVA

Rate of Cyclosporin release can be toggled by altering the VA content and loading level until desired release profile is achieved

- **Experimental**
  - Melt compounding of VitalDose® EVA + Cyclosporin (1203 g/mol) at 80°C
  - Compounded into two different EVAs: 18% & 28% VA
  - Cyclosporin loading levels: 5 & 25 mg (1% & 6% w/w)
- **Summary**
  - Release studied for 30 days from loaded rings in vitro
  - Release rate controlled by VA content

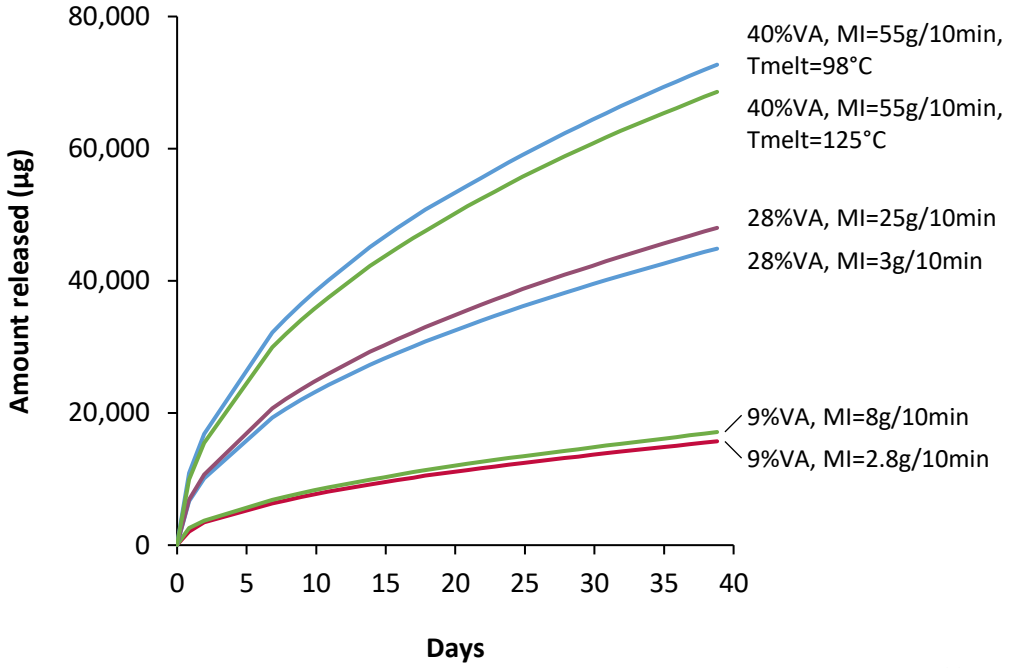


Celanese
The chemistry inside innovation™

Parameters can be tuned to accommodate any API

Niacin release can be tuned by VA content

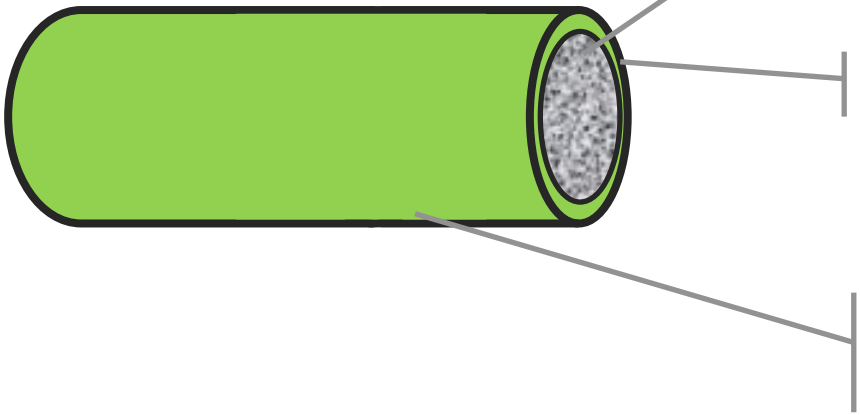
- **Experimental**
  - 5% Niacin loaded EVA
- **Summary**
  - VA content is the dominant variable for determining release rate
  - Release curves do not appear to depend on melt index
  - Adjustments to compounding temperature have minimal impact on release
  - Release fits the Higuchi model which suggests longer term release



Celanese
The chemistry inside innovation™

The ABCs of a Matrix Based Approach

Single or Multiple Drug Design Capabilities



A. High Drug Loading Capabilities

- 80% loading commercial examples
- Excellent physical attributes

B. Functional Membrane

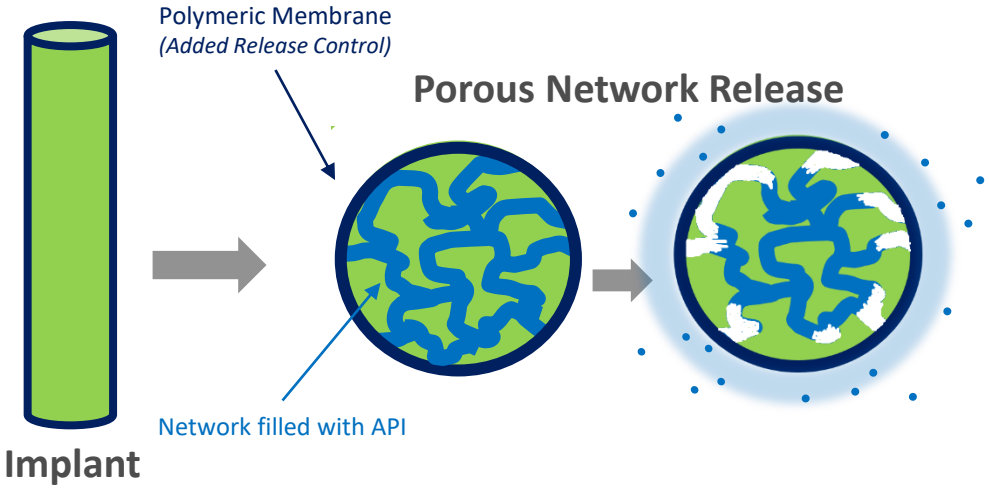
- Additional rate control

C. Technical Design Freedom

- Approach for multidrug release
- Replace or add parts to existing medical devices

Addressing a Wide Range of Drugs and Release Needs

The Broad Capabilities of the VitalDose® EVA Drug Delivery Platform

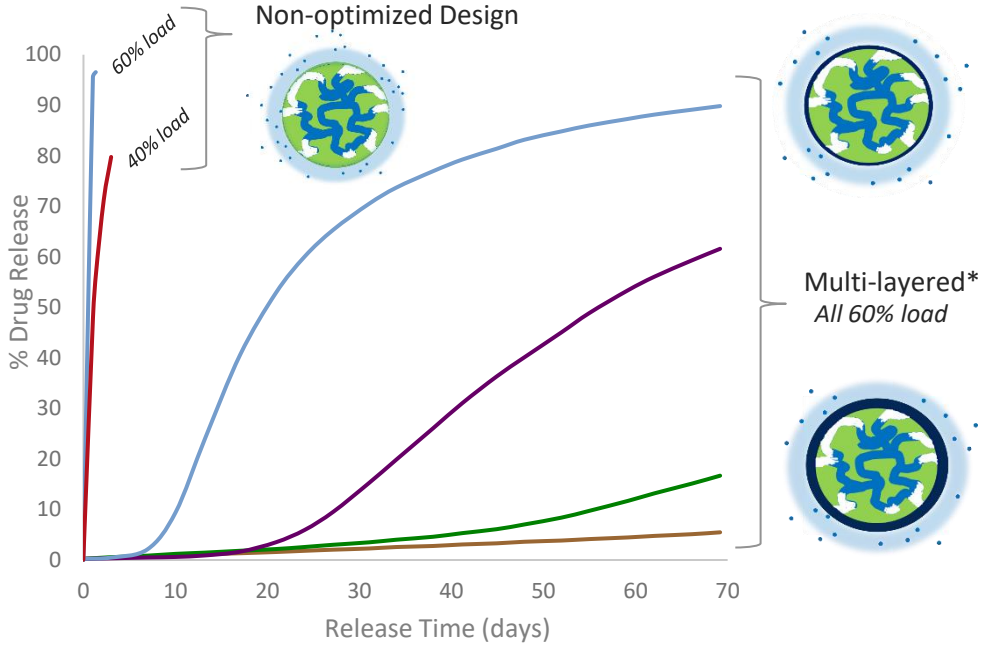


- Sustained release from EVA is possible in either multiple configurations
- Release rate can be tuned by adjusting loading

Celanese
The chemistry inside innovation™

Highly Tunable Drug Release

Addressing a Spectrum of Dosing Kinetic Needs



Flexible design capabilities enable ease of formulation and highly tunable release

Conditions:

- Samples loaded 60% with Lysozyme*
- Release rate varied independent of protein loading

Designs:

- Multiple design configurations allow for customizable range of release rates in biotherapeutics

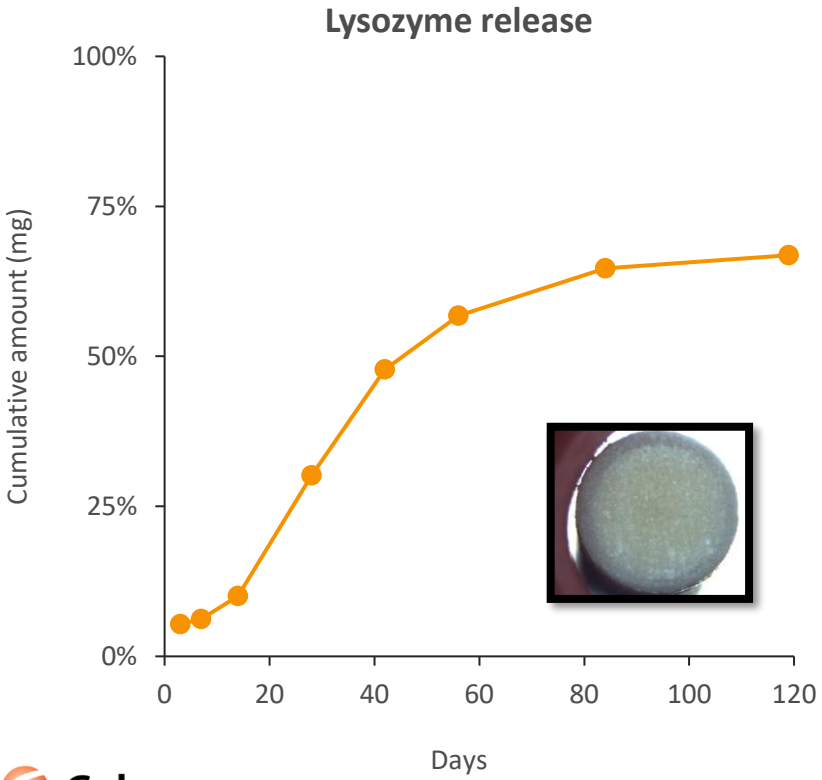
Therapeutic Benefits

Dosing kinetics can be optimized through tunable release

Celanese
The chemistry inside innovation™

Multi-layer Implants via a Scalable Coextrusion Process

Coextrusion was Successfully Conducted at KG Scale



Ease in manufacturing for production on standard equipment

Conditions:

- Coextruded samples loaded 60% with Lysozyme at commercial scale

Designs:

- Multi-layer design allows for implants of a variety of sizes with high loads of sensitive API

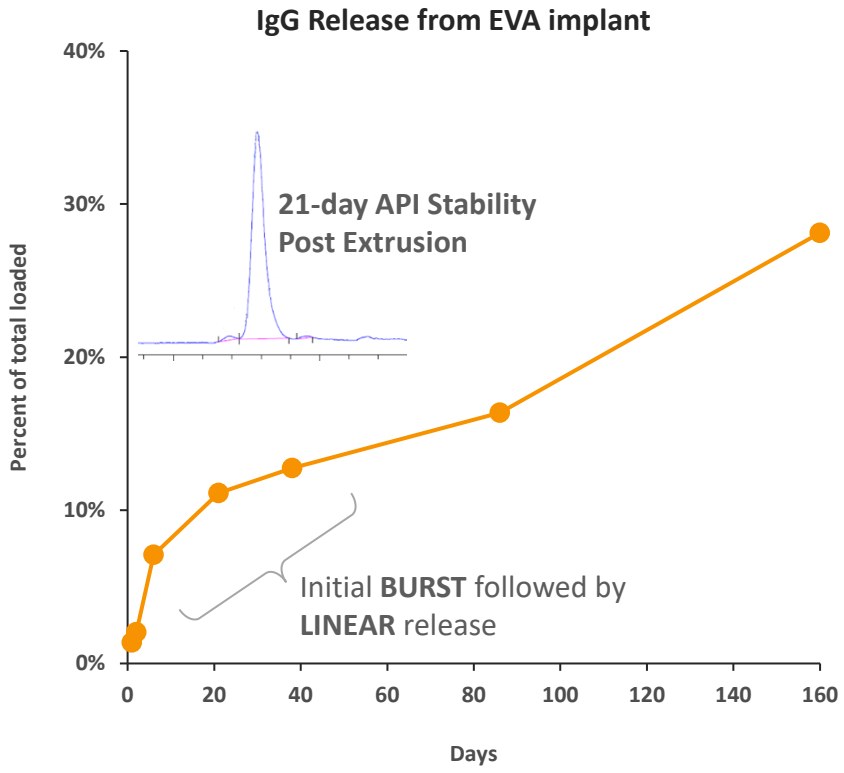
Development Benefits

Scalable process allows for simple tech transfer to seamless commercialization

Celanese
The chemistry inside innovation™

Sustained Release of IgG by porous network from VitalDose® EVA

Potential for Long Acting or Localized Large Biologics Delivery



High MW proteins achieve sustained release for over 5 months

Conditions for implant:

- Implant processed via HME
- Stability confirmed by SEC analysis and ELISA

Results:

- No process degradation of IgG
- Sustained release up to 166 days

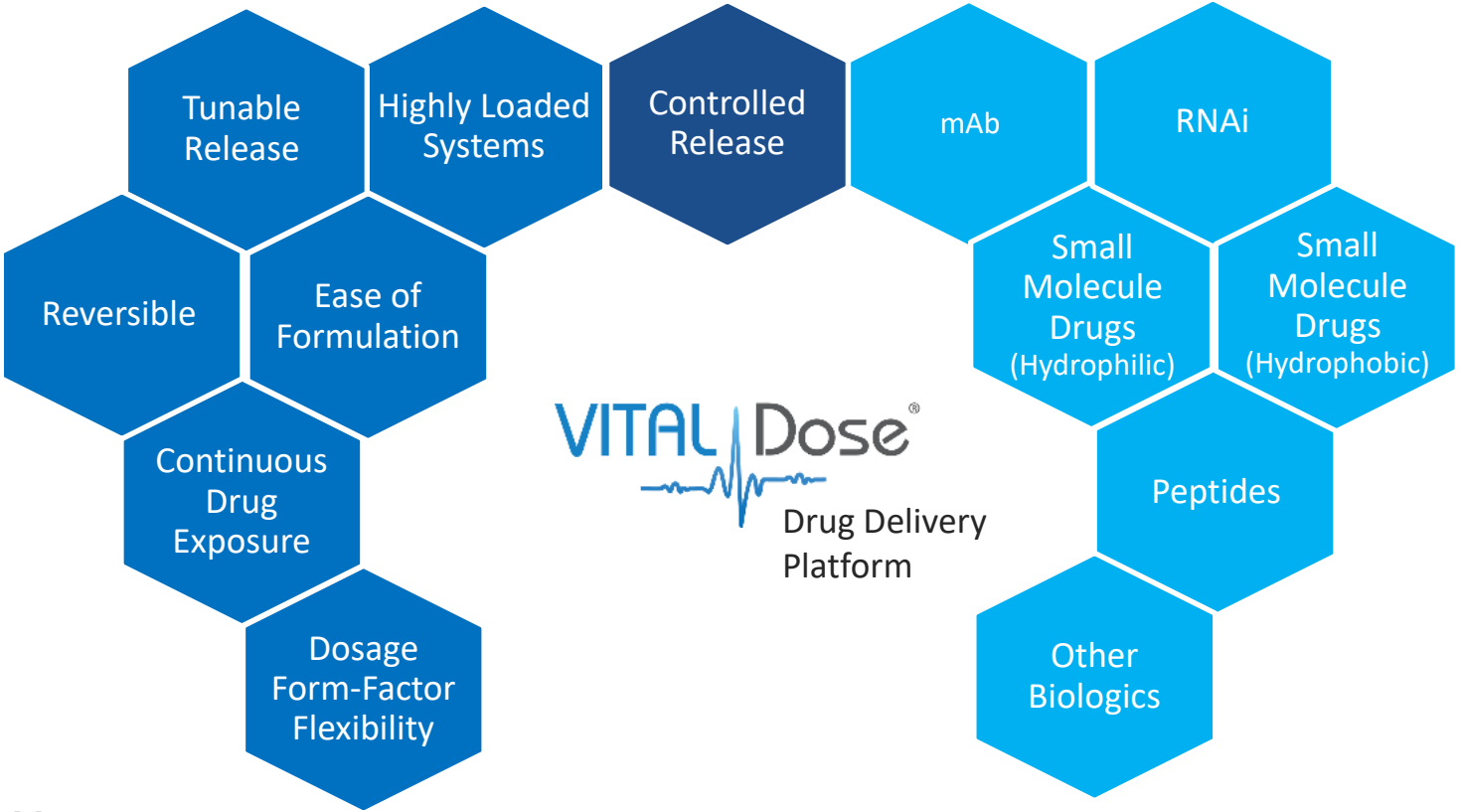
Therapeutic Benefits

Novel depot approach provides a method for any powdered biotherapeutic in oncology, ophthalmology, and other therapeutic areas

Celanese
The chemistry inside innovation™

VitalDose® Drug Platform for Novel Therapeutics

Enabling Better Drug Delivery for Better Treatments



Celanese
The chemistry inside innovation™

VitalDose® EVA can be processed with a range of API amounts to result in various dosage forms and customizable sizes

Intravitreal Implant

<1mg

Ocular Insert

5 – 10mg

Subcutaneous Implant

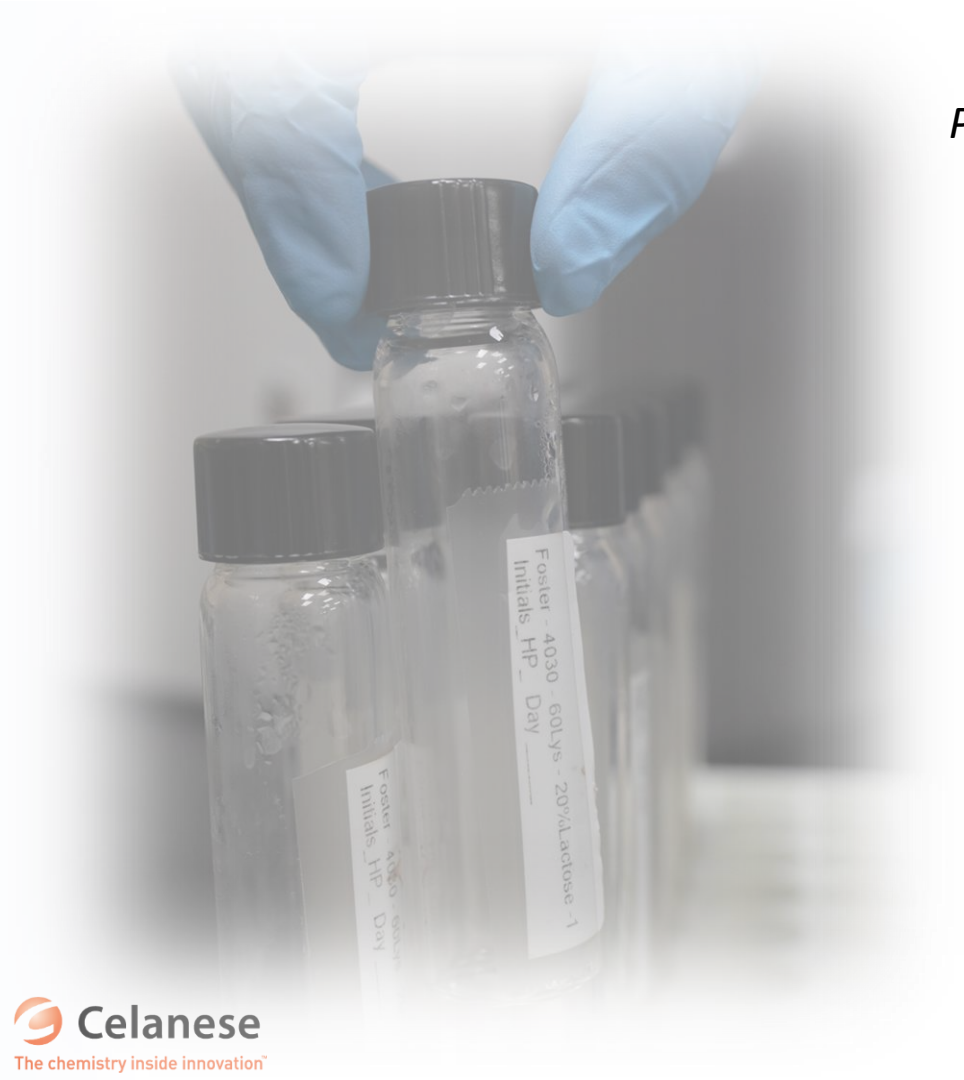
50 – 200mg

Intravaginal Ring

1000 – 2000mg

Range of API amount

Celanese
The chemistry inside innovation™



Development Lab Services

Providing You Support to Demonstrate Feasibility

Paths to Partnership

Development Lab Services

Material Offering & Customization

Celanese
The chemistry inside innovation™

The Celanese Feasibility Lab

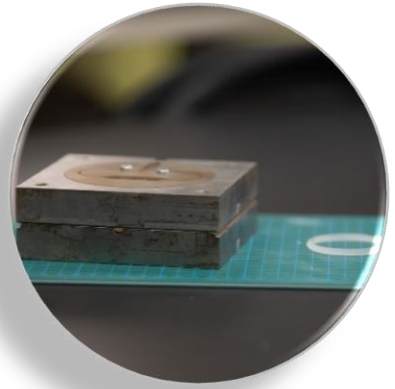
Accelerating your Drug Delivery Programs

Prototype development

Utilize expertise in EVA to match release and design needs

Formulation Development

Recommend ideal material starting points for evaluation and drug development based on years of expertise



Prototyping

Develop prototypes using hot melt extrusion and injection molding

Drug Release Testing

Provide support to achieve your desired release profile

Feasibility testing ✦ Analytical Method Development ✦ Physical characterization ✦ Tech Transfer
CDMO Selection ✦ High-resolution imaging ✦ Mass spectrometry ✦ Chromatography

Celanese
The chemistry inside innovation™

VitalDose® EVA Drug Delivery Platform

Extensive Regulatory History and Support for Your Biologic Drugs

- ☑ Material compliance to FDA and EU requirements
- ☑ Long-term supply assurance without change of formulation
- ☑ Animal- and latex-free formulations
- ☑ Certified biocompatibility (USP 23 Class VI / ISO 10993, etc.)
- ☑ FDA Drug & Device Master Files
- ☑ Individual analytical tests per lot / delivery (purity control) where appropriate
- ☑ Expanded certificate of inspection
- ☑ Change management to GMP-principles
- ☑ Support in Regulatory Approval

Long commercial history of use

Excellent tolerability in multiple parenteral dosage forms

Ability to co-administer large and small molecules from a single implant

Tunable delivery of biologics

Provide development support to achieve your desired release profile

VITAL Dose®

For further support:

Harsh Patel, PhD
Sr. Scientist, Pharma and Medical

Email: harsh.patel@celanese.com
Tel: +01-859-372-3256

Website: https://www.celanese.com/applications/sustained-drug-delivery-technologies

Celanese
The chemistry inside innovation™

Legal Disclaimer

Disclaimer & Notice to Users

This publication was printed based on Celanese's present state of knowledge, and Celanese undertakes no obligation to update it. Because conditions of product use are outside Celanese's control, Celanese makes no warranties, express or implied, and assumes no liability in connection with any use of this information. Nothing herein is intended as a license to operate under or a recommendation to infringe any patents.

Values shown are based on testing of laboratory test specimens and represent data that fall within the standard range of properties for natural material. These values alone do not represent a sufficient basis for any part design and are not intended for use in establishing maximum, minimum, or ranges of values for specification purposes. Colorants or other additives may cause significant variations in data values. Properties of molded parts can be influenced by a wide variety of factors including, but not limited to, material selection, additives, part design, processing conditions and environmental exposure. Any determination of the suitability of a particular material and part design for any use contemplated by the users and the manner of such use is the sole responsibility of the users, who must assure themselves that the material as subsequently processed meets the needs of their particular product or use.

To the best of our knowledge, the information contained in this publication is accurate; however, we do not assume any liability whatsoever for the accuracy and completeness of such information. The information contained in this publication should not be construed as a promise or guarantee of specific properties of our products. It is the sole responsibility of the users to investigate whether any existing patents are infringed by the use of the materials mentioned in this publication. Moreover, there is a need to reduce human exposure to many materials to the lowest practical limits in view of possible adverse effects. To the extent that any hazards may have been mentioned in this publication, we neither suggest nor guarantee that such hazards are the only ones that exist. We recommend that persons intending to rely on any recommendation or to use any equipment, processing technique or material mentioned in this publication should satisfy themselves that they can meet all applicable safety and health standards. We strongly recommend that users seek and adhere to the manufacturer's current instructions for handling each material they use, and entrust the handling of such material to adequately trained personnel only.

The products mentioned herein are not intended for use in medical or dental implants.

Contact Information

Americas
8040 Dixie Highway, Florence, KY 41042 USA
Product Information Service
t: +1-800-833-4882 t: +1-859-372-3244
Customer Service
t: +1-800-526-4960 t: +1-859-372-3214
e: info-engineeredmaterials-am@celanese.com

Europe
Am Unisys-Park 1, 65843 Sulzbach, Germany
Product Information Service
t: +(00)-800-86427-531 t: +49-(0)-69-45009-1011
e: info-engineeredmaterials-eu@celanese.com

Asia
4560 Jinke Road, Zhang Jiang Hi Tech Park
Shanghai 201203 PRC
Customer Service
t: +86 21 3861 9266 f: +86 21 3861 9599
e: info-engineeredmaterials-asia@celanese.com


Celanese
The chemistry inside innovation™