Solving the Medical Polymers Paradox with Ethylene Vinyl Acetate Copolymers for Enabling Advanced Delivery of Proteins and Stem Cells

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\(^2\)Celanese International Corporation, Frankfurt, Germany
Celanese is a global technology and specialty materials company

2014 Net Sales: $6.8B
Employees: 7,500
Manufacturing Locations: 27

Advanced Engineered Materials
$1.5 billion net sales
- Specialty thermoplastics used in automotive, electrical, electronics, more

Acetyl Intermediates
$3.5 billion net sales
- Acetic acid, vinyl acetate monomer, and additional intermediate chemistries

Consumer Specialties
$1.2 billion net sales
- Cellulose derivatives like acetate tow for filters
- Food ingredients including sweeteners, preservatives

Industrial Specialties
$1.2 billion net sales
- Emulsion polymers for paint, adhesives, nonwovens, carpets
- EVA polymers for flexible packaging, medical solutions

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Celanese’s integrated product portfolio

**Building Blocks** → **Differentiated Intermediates** → **Specialty Products**

- **Raw Materials**
  - Acetic Acid
  - Methanol, Olefin, & Acetone Derivatives
  - Anhydride and esters
  - VAM
- **Acetyl Intermediates**
  - Emulsion polymers
  - EVA polymers
  - Cellulose derivatives
  - Food ingredients
  - Engineered Materials
  - Affiliates
  - Specialty Derivatives
- **Industrial Specialties**
- **Consumer Specialties**
- **Advanced Engineered Materials**
Producing polymers since the 1950s, we offer a complete range of grades:

- Ethylene vinyl acetate copolymers
- EVA copolymers up to 40% VA content,
- Broad Melt Index range
- Pharma grades offer long term in the body use
# EVA Applications in Healthcare

## FDA Approvals

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Manufacturer</th>
<th>Active Ingredient</th>
<th>Indication / Application</th>
<th>FDA: NDA / Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progestecert</td>
<td>Alza</td>
<td>Progesterone</td>
<td>Intrauterine device</td>
<td></td>
</tr>
<tr>
<td>Implanon</td>
<td>Organon</td>
<td>Etonogestral</td>
<td>Contraceptive Implant</td>
<td></td>
</tr>
<tr>
<td>Actisite</td>
<td>Alza / J&amp;J</td>
<td>Tetracycline</td>
<td>Periodontitis</td>
<td></td>
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<tr>
<td>Cypher</td>
<td>Cordis / J&amp;J</td>
<td>Serolimus</td>
<td>Vascular Restinosis</td>
<td></td>
</tr>
<tr>
<td>Bravo Matrix</td>
<td>Surmodics</td>
<td>Varies</td>
<td>Stent Coatings / Intravitreal Implants</td>
<td></td>
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</table>
EVA Time Continuum of Healthcare Applications

EVA: Many successful medical applications for many years

1960 – Ethylene vinyl acetate copolymers commercialized

1975 – EVA TPN bag developed as alternative to PVC.

1988 – FDA approves an EVA nutrition bag.

2003 – FDA approves EVA medical bags suitable for cryogenic stem cell storage.

1994 – Market continues to see more EVA products in healthcare

EVA has 40 years of use in the healthcare industry
Boundary Conditions (1)

- Selection criteria: Use EVA copolymers having long and successful FDA approval track record
- Polymer excipient chemistry should be invariant, e.g. no special pendant groups or monomers
- Little to no additives required, if used, additives must be well characterized and have history in previous FDA approved applications
New Agents, Challenges, and Needs in Drug Delivery

Controlled Release Design Space – A need for more degrees of freedom for enabling controlled release of (i) molecular diversity and (ii) release quantities

A comprehensive technology for the delivery of:
- Small molecules: e.g. < 400
- Large molecules: e.g. 40,000 MW
- Complex shaped molecules
- Multi sized molecules
- Staged controlled release
- Microspheres
- High degree of porous microstructure design freedom

Polymer Blends Including Pore Formers – (1) hydrophilic (2) hydrophobic
# EVA – Commercial History with Proteins, Stem Cells

## Cryogenic and FreezeThaw Applications

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Biologics</th>
<th>Stem Cells</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Historical Usage</td>
<td>EVA used in production of proteins</td>
<td>Decades</td>
<td></td>
</tr>
<tr>
<td>Applications</td>
<td>Biopharma Processing, Bioreactor Bags, Media Storage Bags</td>
<td>Cryogenic Stem Cell Storage Bags to -196°C</td>
<td>EVA stem cell storage bags are used in predicate devices and have received FDA 510K approvals.</td>
</tr>
<tr>
<td>Agents</td>
<td>Proteins</td>
<td>Stem cells</td>
<td>High value agents</td>
</tr>
<tr>
<td>Commercially used as contact layer with agents?</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Commercially used in FreezeThaw Cycles</td>
<td>Yes</td>
<td>Yes</td>
<td>Freeze thaw cycling is routine in stem cell applications.</td>
</tr>
<tr>
<td>Sterilization</td>
<td>Gamma</td>
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## New Agents, Challenges, and Needs in Drug Delivery

### BC 1 = BC 2

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<th>Future Reality</th>
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Law of Symmetry of Boundary Conditions: no transformational discontinuities
New Agents, Challenges, and Needs in Drug Delivery

**Need 1:** Non-parenteral biologics delivery

**Need 2:** Biologics delivery in aqueous solution

**Need 3:** Controlled release of biologics (holy grail)

**Need 4:** Improved stability (big need)

**Need 5:** Excellent at freeze–thaw cycling for excipient

**GR oral dosage form:** Lower intestine. Delivery is to gastrointestinal cells for transport to bloodstream.

**Implant:** Deliver stem cells, proteins, Factor IX, Thrombin, or other biologics and small molecules.
Today’s high value agents such as biologics require innovative delivery vehicles.

- **Oral Dosage**
  - Foam Core
  - Enteric coating
  - Docking Layer

- **Implant**
  - Liquid Formulation
  - 3 mm

- **Internal Wound Sealing**

- **Cartilage**
  - Knee Osteoarthritis
  - Destruction of Cartilage
  - Bone on Bone
  - Thinning Cartilage
  - Cartilage
  - Connective Tissue

The Paradox

“Something that is made up of two opposite things and that seems impossible but is actually true or possible”
Merriam - Webster

Medical Polymers Paradox

How does one take a polymer that is decades old, and transform it into a new innovative healthcare solution, without changing it?
Solution: EVA Foamed Excipient Using Supercritical Fluid Microcellular Foaming

API (small molecule) can be incorporated via hot melt extrusion or offline seeding (biologics)

BCS Class II or IV Enhanced Bioavailability
Solution: EVA Foamed Excipient Using Supercritical Fluid Microcellular Foaming

Supercritical Fluid Microcellular Foaming of EVA

- Physical blowing agent
- Inexpensive
- GRAS status
- No residues
- Can ebeam for crosslinking
- Unmodified EVA

sc-N$_2$

$T_C = 126.2K$

$P_C = 3.4$ MPa
Microcellular foaming with the MuCell process

Typical morphology of microcellular foam structure:
Sandwich structure, closed-cell,

SCF dosing system
Gas supply
\([N_2, CO_2]\)

Pressure control module
SCF
SCF injectors

100 micron

Trexel Corp.
Experimental Data

- Injection-molded EVA foam
  - Inert sc-N₂ gas as blowing agent
  - Additives: avoided or GRAS
- Foam structure: semi-open
  - Density reduction: 78 %
  - Pore size: 450 ± 100 nm

- 200kD PSS as water soluble model API
- Seeding of foam samples: 1 wt.-% PSS sol.

- Release profiles measured in 37°C HBSS solution via UV/Vis

Sodium-p-styrenesulfonate
Experimental Data

sodium poly (styrene sulfonate) 200kD in HBSS at 37°C

Release from interior “reservoir”

Release from outer deposits
Overview of Solution to the Medical Polymers Paradox using EVA sc-MCF Foamed Excipient

BC 1 = BC 2

Current Reality: Controlled Release Small Molecules

- Use EVA copolymers with long and successful FDA approval track record
- Chemistry is invariant, e.g. no special pendant groups or monomers
- Little to no additives required, if used, well characterized and used in previous FDA approved applications

Future Reality: Controlled Release Biologics & Stem Cells

- Use EVA copolymers with long and successful FDA approval track record
- Chemistry is invariant, e.g. no special pendant groups or monomers
- Little to no additives required, if used, well characterized and used in previous FDA approved applications

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Law of Symmetry of Boundary Conditions: no transformational discontinuities
Seeking partners for collaboration

Immunogenicity of Therapeutic Proteins

• Very important problem in biologics drug delivery
• Solutions sought and better understanding required
• More alternative administration routes sought for enhancing mitigation
• High dose parenteral administration versus low dose controlled release
• Improved stability is of interest and value

Can an innovative delivery vehicle like EVA Foamed Excipient mitigate immunogenicity by offering new routes of administration, enhanced dosing and stability?
Conclusions and Outlook

• Controlled release of 200,000 Dalton model API (simulated mAb)
• Aqueous delivery containing the agent was demonstrated
• EVA foamed excipient delivered large molecules in non-parenteral administration mode
• We are continuing our work on
  …engineering of the microcellular foam structure
  …adjusting the release time scales
  …testing for safety & toxicology requirements
  …creating specific controlled release solutions
  …BSA agent under testing
• Whitepapers available: www.vitaldose.com
A call to action…

Moving the Innovation Frontier for Transitioning Future Reality into Current Reality

EVA Current Reality
- Small molecule delivery
- Stem cell storage
- Biopharma processing
- Medical devices

Future Reality
- EVA Controlled Release of Biologics and Cells of High Value

Market Space

Time
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