Excipients as Absorption Enhancers For Drug Delivery Applications

(A Case Study Using Vitamin E TPGS, NF)

Presented by

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Eastman Chemical Company
Need and Concerns for Using Absorption Enhancers in Drug Delivery Systems

• Many new drug candidates exhibit poor water-solubility, poor permeability, and thus poor bioavailability.

• Solubilizing the drug in a liquid, solid or semi-solid (soft gel capsule) formulation is needed.

• Main concerns are effectiveness, mechanism and toxicity.
Outline

1. An overview of drug solubilization and absorption enhancers
2. Structure and typical properties of vitamin E TPGS
3. Known applications
4. Milestones in the development of vitamin E TPGS
5. Thermal properties
6. Liquid crystalline and solution properties
7. Mechanism of absorption enhancement
8. An example: Amprenavir (Agenerase™ by Glaxo Wellcome in 1999)
9. References and patent art
Critical Issues of Using Absorption Enhancers

- Effectiveness of bioavailability enhancement
  - Effective concentration at the site of absorption
  - Site-dependent
  - Inter-subject variability
  - Formulation and physiologic variables
- Mechanism of permeation enhancement
- Toxicity
Vitamin E TPGS NF

• Water-miscible form of vitamin E derivative
• Structure-property relationship suggests that it may uniquely meet the need for enhancing drug solubility, permeability, safety and hence bioavailability
Eastman Vitamin E TPGS NF
(d-Alpha Tocopheryl Polyethylene Glycol 1000 Succinate)
Key Attributes of Vitamin E TPGS

- Average MW ~ 1513
- Waxy solid m.p. 37 - 41 °C
- Water-miscibility miscible in all parts
- Solubility in PEG 400 miscible
- HLB Value ~13.2
- Liquid crystal structures solution ↔ gel
- Stability in aqueous media stable at pH 4.5 - 7.5 hydrolyzed in the body
- Vitamin E Content 260 mg/g (387 IU/g)
Milestones in the Development of Vitamin E TPGS NF for Absorption Enhancement and Drug Delivery Applications

- 1950 Water-soluble vitamin E TPGS invented by Eastman Kodak Co.
- 1960 Suggested as a solubilizing agent for oil-soluble vitamins
- 1970 Toxicity and the effects on reproduction in rats studies
- 1980 Using TPGS for treating vitamin E deficient patients suggested for treating chronic cholestasis demonstrated for treating vitamin E deficiency in animals demonstrated
- 1990 Useful as a water-soluble antioxidant (effective after hydrolysis) Enhanced cyclosporin absorption demonstrated Enhanced vitamin D absorption demonstrated
- 1995 Mechanism of enhancing cyclosporin absorption suggested Liquid crystalline properties characterized and reported
- 1996 TPGS as a P-glycoprotein inhibitor suggested Many application patents appeared
- 1999 Amprenavir commercialized (semi-solid dosage forms) Vitamin E TPGS NF listed as an excipient in USP 24 (1999)
- 2000 Absorption enhancer for poorly absorbed drugs
Applications of Vitamin E TPGS NF in Drug Delivery Systems

1. Solubilize drugs
2. Prevent drugs from crystallization
3. Protect drugs in the absorption process
4. Enhance bioavailability of poorly absorbed drugs
5. Reduce drug sensitivity on skin or tissues
6. A vehicle in a semi-solid dosage form
7. Provide vitamin E or poorly soluble nutriceuticals in liquid dosage form
8. An emulsifier for injectable formulation
9. A vehicle for pulmonary (inhalation) dosage form
10. A functional ingredient in self-emulsifying formulations
11. A carrier for wound care and treatment
12. A thermal binder in melt granulation/extrusion process
Melting Temperature of TPGS

1. 1st Heat Cycle
2. 2nd Heat Cycle
3. 10th Heat Cycle
4. 20th Heat Cycle
Thermal Stability of TPGS

Degradation Temperature = 200.0 °C
TPGS Under Sterilization Condition at 125 °C
## Stability of Vitamin E TPGS NF at 60°C

<table>
<thead>
<tr>
<th>Sample</th>
<th>Acid Value</th>
<th>Gardner Color</th>
<th>Free Tocopherol (mg/g)</th>
<th>Potency, mg/g alpha Tocopherol</th>
<th>Melting Point, °C</th>
<th>Degradation Temperature, °C</th>
</tr>
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<tbody>
<tr>
<td>Time 0</td>
<td>0.30</td>
<td>4.3</td>
<td>5</td>
<td>262</td>
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<tr>
<td>Day 1</td>
<td>0.35</td>
<td>4.2</td>
<td>6</td>
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<tr>
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<td>4.2</td>
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<td>215</td>
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<tr>
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<td>5</td>
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<td>40</td>
<td>212</td>
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</table>
## Vitamin E TPGS NF Stability
### Ambient Stored as Packaged

<table>
<thead>
<tr>
<th>Time (mos.)</th>
<th>Acid Value</th>
<th>Gardner Color</th>
<th>Alpha Tocopherol (mg/g)*</th>
<th>Free Tocopherol</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>0.6</td>
<td>2+</td>
<td>290</td>
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<tr>
<td>1</td>
<td>0.6</td>
<td>3</td>
<td>300</td>
<td>5</td>
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<tr>
<td>2</td>
<td>0.6</td>
<td>3</td>
<td>292</td>
<td>3</td>
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<tr>
<td>3</td>
<td>0.8</td>
<td>3</td>
<td>288</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>0.8</td>
<td>2+</td>
<td>290</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>0.6</td>
<td>3</td>
<td>287</td>
<td>5</td>
</tr>
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<td>0.9</td>
<td>3+</td>
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<td>0.7</td>
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<td>292</td>
<td>4</td>
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<tr>
<td>19</td>
<td>0.8</td>
<td>2+</td>
<td>Not Tested</td>
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<tr>
<td>29</td>
<td>1</td>
<td>3</td>
<td>289</td>
<td>3</td>
</tr>
</tbody>
</table>

*d-alpha tocopherol content after saponification*
Melt Viscosity of Vitamin E TPGS NF

Temperature, °C

Viscosity*, centipoise

*using Brookfield viscometer with spindle no. 21
Thermal Properties of TPGS

- Melting temperature: 37 - 41°C
  Thermal degradation temperature: 200°C
- Stable under heat sterilization condition at 125°C for at least one hour
- Stable as a liquid at 60 - 75°C for at least three days
- Stable as packaged at ambient storage conditions for more than 2 years
- Low melt viscosity at ~ 75°C for ease of handling
Surface Tension of TPGS at 37 °C

Surface Tension (dyne/cm)

CMC = 0.02 wt %
Relative Viscosity of TPGS in Water

Temperature
- 20 °C
- 25 °C
- 30 °C
- 35 °C
- 40 °C

Hard Sphere

Relative Viscosity vs. Volume Fraction at Different Temperatures
Viscosity Behavior of TPGS/Water System

Model R-Square = 96%, Root Mean Square Error = 4.8
Stability of TPGS in 10% Aqueous Solutions*

*Stored at 40 °C, 75% RH
Structure of Lipid Aggregates in Water
Phase Behavior of TPGS/Water Blends at 37 °C

Increasing Water Content

<table>
<thead>
<tr>
<th>Normal Molar Phase</th>
<th>Mixed Phase</th>
<th>Hexagonal Phase</th>
<th>Mixed Phase</th>
<th>Reversed Molar Phase</th>
<th>Lamellar Phase</th>
</tr>
</thead>
</table>

Symbols and images illustrating the different phases.
Properties Of TPGS In Water

- TPGS is surface active
  CMC = 0.02 wt. % at 37 °C
- TPGS is a good emulsifier
- TPGS in water forms liquid crystalline phases
- TPGS in water has a wide viscosity range
- TPGS is chemically stable in neutral aqueous media
Drug Absorption Mechanisms

How does TPGS enhance bioavailability of certain classes of poorly water-soluble or poorly absorbed drugs?
Effect of Water-soluble Vitamin E\(^1\) on Oral Cyclosporin\(^2\) in 10 Healthy Volunteers


\[
\frac{F_{\text{CYA + TPGS}}}{F_{\text{CYA}}} = 1.58 \pm 0.24
\]

\(^1\)Vitamin E TPGS 2.6 IU/kg

\(^2\)Cyclosporin 10 mg/kg
A: Paracellular diffusion
B: Paracellular diffusion enhanced by a modulator of tight junctions
C: Transcellular passive diffusion; C*: Intracellular metabolism
D: Carrier-mediated transcellular transport
E: Transcellular diffusion modified by an apically polarized efflux mechanism
F: Transcellular vesicular transcytosis
## Mechanisms of Drug Transport Across GI Absorptive Epithelia

<table>
<thead>
<tr>
<th>Route</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transcellular passive diffusion</strong></td>
<td>Propranol</td>
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<tr>
<td></td>
<td>Testosterone</td>
</tr>
<tr>
<td></td>
<td>Ketoprofen</td>
</tr>
<tr>
<td></td>
<td>Cisapride</td>
</tr>
<tr>
<td></td>
<td>Estradiol</td>
</tr>
<tr>
<td></td>
<td>Naproxen</td>
</tr>
<tr>
<td><strong>Paracellular passive diffusion</strong></td>
<td>Cimetidine</td>
</tr>
<tr>
<td></td>
<td>Loperamide</td>
</tr>
<tr>
<td></td>
<td>Atenolol</td>
</tr>
<tr>
<td></td>
<td>Mannitol</td>
</tr>
<tr>
<td></td>
<td>Berberine</td>
</tr>
<tr>
<td></td>
<td>Berberine</td>
</tr>
<tr>
<td></td>
<td>Tiludronate</td>
</tr>
</tbody>
</table>
## Mechanisms of Drug Transport Across GI Absorptive Epithelia

<table>
<thead>
<tr>
<th>Route</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carrier-mediated transcellular diffusion</strong></td>
<td>Cephalexin</td>
</tr>
<tr>
<td></td>
<td>Captopril</td>
</tr>
<tr>
<td></td>
<td>Bestatin</td>
</tr>
<tr>
<td></td>
<td>Levodopa</td>
</tr>
<tr>
<td></td>
<td>Foscarnet</td>
</tr>
<tr>
<td></td>
<td>Loracarbef</td>
</tr>
<tr>
<td><strong>Transcellular diffusion subject to P-Glycoprotein efflux</strong></td>
<td>Cyclosporin</td>
</tr>
<tr>
<td></td>
<td>Nifedipine</td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
</tr>
<tr>
<td></td>
<td>Celiprolol</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
</tr>
<tr>
<td></td>
<td>Taxol</td>
</tr>
</tbody>
</table>
Model of Drug Absorption in the Presence of Both P-Glycoprotein and Cytochrome P450 3A.
Model of P-Glycoprotein Substrate Absorption

A generase™ [Amprenavir (APV)]

(Lawrence Yu et. al, Pharm. Res. 16(12), p. 1812, 1999)

• A HIV protease inhibitor, used in AIDS therapy
• The current clinical approach to HIV therapy utilizes a combination regimen consisting of a protease inhibitor with other reverse transcriptase inhibitors
• APV has a low solubility in water and is poorly wetted
• Conventional oral formulations (capsules and tablets) had no detectable drug in the blood after administration
• The current estimate of the daily dose is high (1200 mg/b.i.d.)
Structure and pH-Solubility of Amprenavir Free Base

pKa = 1.97
Solubility Data Analysis and Results

$$APV + (TPGS)_m \leftrightarrow APV - (TPGS)_m$$

$$k_a = \frac{S_{bound}}{S_{free} \cdot (TPGS)_m}$$

$$S_{total} = S_{free} + S_{bound}$$

$$S_{total} = S_{free} [1 + k_a (TPGS)_m]$$

CMC = 0.20 mg/mL
Permeability Results
(Caco-2 Cell Model)

Apparent permeability x 10^6 (cm/sec) vs TPGS concentration (mg/mL)
Absorption Flux for Amprenavir

Absorption flux (mg/cm²/sec x 10⁻⁶) vs. TPGS concentration (mg/mL)

- Absorption flux increases with increasing TPGS concentration.
- The graph shows a positive trend from 0.0 to 0.9 mg/cm²/sec x 10⁻⁶.
- The TPGS concentration ranges from 0.0 to 2.0 mg/mL.

Key Observations:
- Initial increase in absorption flux is rapid.
- Slower increase observed at higher TPGS concentrations.
- Maximum absorption flux observed at 2.0 mg/mL TPGS concentration.
Role of TPGS in Improving Bioavailability of Amprenavir

• The solubility of Amprenavir was improved in the presence of TPGS through micellar solubilization

• TPGS also enhances the permeability of Amprenavir

• Overall, TPGS enhanced the absorption flux of Amprenavir by increasing its solubility and permeability
## Examples of TPGS Applications in Patent Art

<table>
<thead>
<tr>
<th>Year</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>1954</td>
<td>Solubilizing agent</td>
</tr>
<tr>
<td>1963</td>
<td>Emulsifying agent</td>
</tr>
<tr>
<td>1987</td>
<td>Application utilizing compatibility with nasal mucosal membrane</td>
</tr>
<tr>
<td>1993</td>
<td>Cytoprotective agent</td>
</tr>
<tr>
<td></td>
<td>Improved bioavailability</td>
</tr>
<tr>
<td></td>
<td>Powder formulation</td>
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<tr>
<td></td>
<td>Topical treatment of sunburn</td>
</tr>
<tr>
<td>1994</td>
<td>Coating additive</td>
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<tr>
<td>1995</td>
<td>Solubilizing poorly water-soluble drugs (transmucosal)</td>
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<tr>
<td>1996</td>
<td>Skin treatment</td>
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<td>Ophthalmic formulations</td>
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<td>1997</td>
<td>Topical homeostatic application</td>
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<td>1998</td>
<td>Oral insulin delivery</td>
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<tr>
<td>1999</td>
<td>Drug delivery using liquid crystalline structures</td>
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<tr>
<td>2000</td>
<td>Specific absorption enhancement applications</td>
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