The Properties and Functions of Vitamin E TPGS

Vitamin E polyethylene glycol succinate

Nigel Langley
ExcipientFest 2015

Introduction

The need for solubilizers

<table>
<thead>
<tr>
<th>Class</th>
<th>Solubility</th>
<th>Permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>0.1 mg/mL</td>
<td>70%</td>
</tr>
<tr>
<td>I</td>
<td></td>
<td>5%</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td>20%</td>
</tr>
<tr>
<td>III</td>
<td></td>
<td>5%</td>
</tr>
</tbody>
</table>

About 95% of all new chemical entities (NCE) show poor solubility and/or poor permeability.
Enhancement of “Biopharmaceutical Fitness”

Enhancement of solubility
- pH-adjustment
- co-solvents
- surfactant systems (incl. SEDDS)
- complexation
- micronization / nano
- …

Enhancement of permeability
- tight junction openers
- metabolic inhibitors
- motility modifier
- pro-drugs
- efflux inhibitors (P-gp)

Excipients with various functions are useful to increase biopharmaceutical fitness of Class II-IV substances

Vitamin E TPGS
Kolliphor™ TPGS

Chemical composition

- Kolliphor™ TPGS is produced by esterification of natural vitamin E succinate with polyethylene glycol (1,000 Da)
- It contains high amounts of mono-ester (main component ~87%), but also di-esters (~7%) and free PEG (~2-3%)
- Mw~1,500 Da (main component); potency of vitamin E ~420 I.U./g
### Overview of properties

<table>
<thead>
<tr>
<th>Properties</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Names</strong></td>
<td>Vitamin E polyethylene glycol succinate (USP)</td>
</tr>
<tr>
<td></td>
<td>Tocopherol (INCI / INN)</td>
</tr>
<tr>
<td></td>
<td>TPGS, Tocofersolan, vitamin E TPGS (Synonyms)</td>
</tr>
<tr>
<td><strong>Appearance</strong></td>
<td>White to light brown waxy solid</td>
</tr>
<tr>
<td><strong>Gardner color</strong></td>
<td>Max. 10 (usually ~3)</td>
</tr>
<tr>
<td><strong>Vitamin E content</strong></td>
<td>260 – 300 mg/g (as D-α-tocopherol)</td>
</tr>
<tr>
<td><strong>Melting point</strong></td>
<td>37 – 40 °C</td>
</tr>
<tr>
<td><strong>Specific gravity</strong></td>
<td>Approx. 1.06 (45 °C)</td>
</tr>
<tr>
<td><strong>HLB value</strong></td>
<td>Approx. 13</td>
</tr>
<tr>
<td><strong>Critical micelle concentration (CMC)</strong></td>
<td>0.02 %/(m/m) at 37 °C (surface tension method)</td>
</tr>
<tr>
<td><strong>Solubility in water</strong></td>
<td>Miscible in all parts</td>
</tr>
<tr>
<td><strong>Dynamic viscosity</strong></td>
<td>1.5 mPa*s (22 °C; 5% solution in water)</td>
</tr>
</tbody>
</table>

### Kolliphor® TPGS resists stress

- **Crystallization:** 24h @ RT
- **Melting:** 24h @ 65°C
Kolliphor® TPGS resists stress

- Melting
- Keep for 5 days at 80°C
- Cool down and analyse

Thermal properties – Melting Point

TPGS was not pre-conditioned prior DSC measurement
Specific Heat Capacity and thermal stability of Kolliphor® TPGS

- Thermally stable until 200°C
- Flash point (DIN EN ISO 2592): 286°C
- Inflammation point: 384°C

**By the way – how does TPGS crystallize?**

- Cooling from outside to inside
- Decreasing Volume
- Nuclei growth
- Nuclei formation on surface

Timelapse video wraps 5h into 20s
**Fields of Application**

<table>
<thead>
<tr>
<th>Enhancement of Bioavailability</th>
<th>Excipient in melt extrusion</th>
<th>Source of natural vitamin E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase solubility of poorly water-soluble APIs</td>
<td>Versatile plasticizer with solubilization properties</td>
<td>For patients suffering from vitamin E malabsorption (cholestatic disease)*</td>
</tr>
<tr>
<td>Formulation of SEDDS</td>
<td>Antioxidant for sensitive excipients</td>
<td>Water-soluble vitamin E in dietary supplements</td>
</tr>
</tbody>
</table>

*GMP production according to ICH Q7 needed

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**High Throughput Screening (HTS)**

Effective and fast screening of solubilization capacity of different solubilizers for various APIs
Status Set up of HTS
*UV testing method is integrated*

**Testing**
- UV/VIS detection
- automatic dilution
- modular set up allows integration of a variety of analytical tools

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Increase of solubility

*Source: BASF / Determination of thermodynamic solubility with a high-throughput robot*

- Massive increase of solubility was observed for all tested APIs (Solu-HTS)
- No dependency on chemical structure
- Almost linear increase of solubility and concentration for most APIs
Solid dispersions of furosemide and TPGS were prepared by solvent method using methanol.

- Amorphous state of solid dispersion was proven by XRD and thermal analysis.
- Dissolution rate and speed was markedly enhanced for solid dispersion compared to pure API and to physical mixture.

Paclitaxel solubility is significantly increased by TPGS (left).

Oral bioavailability of Paclitaxel is enhanced in combination with TPGS (right).
Increased absorption flux of Amprenavir

L. Yu et al., Pharm. Res., 16 (1999), 1812-1817

- Above its CMC TPGS increases solubility of Amprenavir linearly (left)
- TPGS also inhibits the efflux system
- As a result of both, the absorption flux of Amprenavir is increased (right)

Improve of processability


- TPGS acts as plasticizer for HPC/PEO combinations and reduces the glass transition temperature (left)
- Lower degradation during extrusion is achieved (GPC, right)
**Properties of film extrudates**


- Elongation at break of extruded HPC/PEO films increases with increasing amounts of TPGS (left).
- Increase of elongation is much higher than with conventional plasticizers (TEC, ATBC), however little lower compared to PEG 400 (right).

**Vitamin E for malabsorbing patients**

K. Papas, Dig. Dis. Sci., 52 (2007), 347-352

- A TPGS formulation (Aqua-E) was compared to an oily formulation (Soft gel) of vitamin E.
- Children, suffering from cystic fibrosis, showed massively enhanced plasma levels of tocopherol after intake of TPGS formulation.
- AUC values were about three times higher for TPGS formulation compared to oily formulation.
Inactive ingredient database lists several approved drug products.

Besides oral solutions and capsule formulations also ophthalmic and topical solutions are found.

**Search Results for: "Tocophersolan"**

<table>
<thead>
<tr>
<th>INACTIVE INGREDIENT</th>
<th>ROUTE/DOSAGE FORM</th>
<th>CAS NUMBER</th>
<th>UNII</th>
<th>MAXIMUM POTENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOCOPHEROL OLAY</td>
<td>OPHTHALMIC SOLUTION, DROPS</td>
<td>9002954</td>
<td>003599U1F2</td>
<td>0.5%</td>
</tr>
<tr>
<td>TOCOPHEROL OLAY</td>
<td>ORAL, CAPSULE</td>
<td>9002954</td>
<td>003599U1F2</td>
<td>300MG</td>
</tr>
<tr>
<td>TOCOPHEROL OLAY</td>
<td>ORAL, CAPSULE, SOFT GELATIN</td>
<td>9002954</td>
<td>003599U1F2</td>
<td>282MG</td>
</tr>
<tr>
<td>TOCOPHEROL OLAY</td>
<td>ORAL, SOLUTION</td>
<td>9002954</td>
<td>003599U1F2</td>
<td>12%</td>
</tr>
<tr>
<td>TOCOPHEROL OLAY</td>
<td>ORAL, TABLET</td>
<td>9002954</td>
<td>003599U1F2</td>
<td>0.03MG</td>
</tr>
<tr>
<td>TOCOPHEROL OLAY</td>
<td>TOPICAL SOLUITION, DROPS</td>
<td>9002954</td>
<td>003599U1F2</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Update Frequency: Quarterly
Data Through: September 16, 2013
Database Last Updated: October 24, 2013

**Products using Tocophersolan**

- **Vedrop**
  - 50 mg/ml oral solution
  - Each ml contains 50 mg of d-alpha-tocopherol, in the form of tocfersolan, corresponding to 74.5 IU of tocopherol.

- **APTIVUS**
  - Oral solution
  - Tipranavir, protease inhibitor of HIV-1
  - Each milliliter of APTIVUS oral solution contains 116 IU of vitamin E, and when taken at the recommended maximum dose of 500 mg/200 mg tipranavir/ritonavir BID results in a daily dose of 1160 IU.

- **AGENERASE**
  - Soft gel capsules
  - Amprenavir
  - The total amount of vitamin E in the recommended daily adult dose of AGENERASE is 1,744 IU.
Products using Tocophersolan

<table>
<thead>
<tr>
<th>Agenerase Oral Solution</th>
<th>Viekira Pak tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solution contains 46 IU vitamin E in the form of TPGS. Propylene glycol is in the formulation to achieve adequate solubility of amprenavir.</td>
<td>Treats Hepatitis C Ombitasvir, Paritaprevir, Ritonavir Fixed-Dose Combination tablet contains copovidone, vitamin E polyethylene glycol succinate…</td>
</tr>
</tbody>
</table>

Upper intake levels (UL) for vitamin E

<table>
<thead>
<tr>
<th>Age</th>
<th>Male (I.U.)</th>
<th>Female (I.U.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 years</td>
<td>200 mg (300 I.U.)</td>
<td>200 mg (300 I.U.)</td>
</tr>
<tr>
<td>4-8 years</td>
<td>300 mg (450 I.U.)</td>
<td>300 mg (450 I.U.)</td>
</tr>
<tr>
<td>9-13 years</td>
<td>600 mg (900 I.U.)</td>
<td>600 mg (900 I.U.)</td>
</tr>
<tr>
<td>14-18 years</td>
<td>800 mg (1,200 I.U.)</td>
<td>800 mg (1,200 I.U.)</td>
</tr>
<tr>
<td>19+ years</td>
<td>1,000 mg (1,500 I.U.)</td>
<td>1,000 mg (1,500 I.U.)</td>
</tr>
</tbody>
</table>

- The maximum daily intake of TPGS is probably set by the vitamin E content
- Recommended dietary allowance for vitamin E is quite low: 15 mg (~23 I.U.) for adults
- However, the upper intake levels are much higher: 1,000 mg for adults irrespective of gender
- This corresponds to a maximum daily intake of ~3.5 g for TPGS
Enhances bioavailability of poorly soluble APIs
Improves processability in melt extrusion
Serves as effective, non-acidic antioxidant
Delivers water-soluble, natural vitamin E