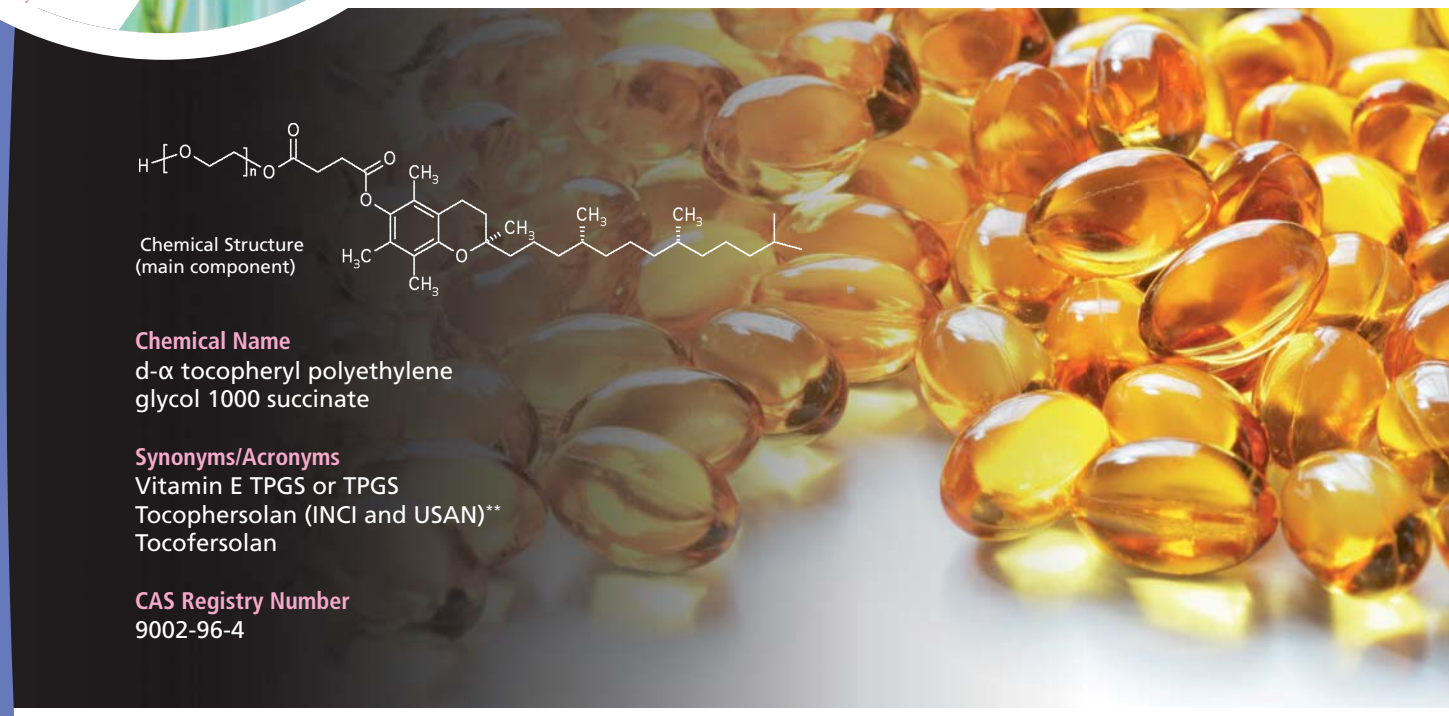
Vitamin E TPGS

NF* and Food Grade



Chemical Structure
(main component)

Chemical Name
d-α tocopheryl polyethylene glycol 1000 succinate

Synonyms/Acronyms
Vitamin E TPGS or TPGS
Tocophersolan (INCI and USAN)**
Tocofersolan

CAS Registry Number
9002-96-4

Isochem Vitamin E TPGS is a multi role excipient used in nutraceutical and pharmaceutical applications. Vitamin E TPGS has shown proven and recognized properties to improve **bioavailability** of poorly absorbed drugs vitamins micro-nutrients acting as an **absorption and permeability** enhancer and to developp Self Emulsifying Drug Delivery System (SEEDS) for poorly soluble drugs as an emulsifier. As a water soluble compound, Vitamin E TPGS is also used as an efficient source of natural Vitamin E, both for therapeutic purposes and nutrition. In Addition Vitamin E TPGS has physical properties that make it a relevant plasticizer for innovative technologies in the pharmaceutical industry such as hot melt extrusion.

APPLICATIONS

- Pharmaceutical and Nutraceutical application
- Nutritional supplements
- Food and beverage
- Cosmetic
- Personal care
- Animal nutrition

*NF: National Formulary (US)
** INCI: International Nomenclature of Cosmetic Ingredients - USAN United States Adopted Names

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Isochem vitamin E TPGS is prepared by esterification of the carboxylic group of crystalline d-α-tocopheryl succinate with polyethylene glycol 1000. The manufacturing process is fully validated.

Isochem Vitamin E TPGS is manufactured in France in state of the art **FDA audited cGMP facilities.** Isochem has been granted a certificate of GMP compliance for the production of Vitamin E TPGS by the French Drug Authorities, ANSM (Agence Nationale de Sécurité du Médicament).

Isochem offers to the market a production capacity in **hundred of tons** scale added to supply chain security of **two qualified production sites.**

Isochem has multi sourced approvals of key raw materials complying with Pharamacopeia in order to secure its supply chain.

Other quality statments

- Meeting kosher certification requirements
- Ingredients free of GMO (Genetic Modified organisms) and BSE/TSE (Bovine Spongiform Encephalopathy / Transmittable Agents of Animal Spongiform Encephalopathy).
- Certificates are available upon request

Safety and toxicology

A large number of studies to address the safety of Vitamin E TPGS have been conducted in the last decades both in humans and in animals (see references page 4). Studies to assess the safety and bioavailability of Vitamin E TPGS for use in food particularly for nutritional/medical purposes have been conducted by EFSA (European Food Safety Authority) (EFSA Journal (2007) 490, 1-20). From toxicology studies, an overall no-observed-adverse-effect level (NOAEL) of 1000mg/kg body weight per day can be derived. Vitamin E TPGS is not genotoxic.



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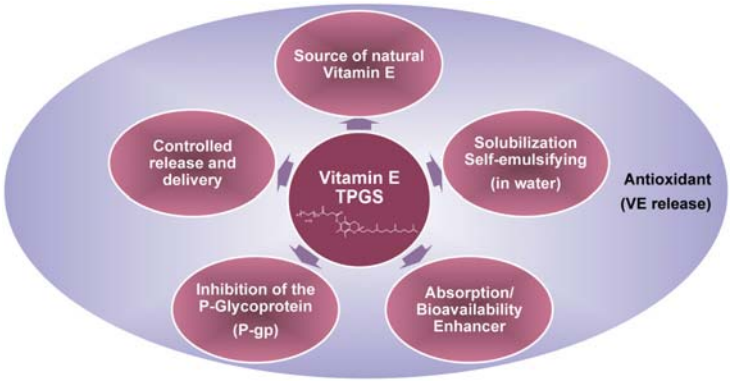
FORMULATION USING VITAMIN E TPGS

A lot of pharmaceutical companies have incorporated Vitamin E TPGS mainly in oral dosage forms for years but new delivery applications are being investigated:

- parenteral delivery
- topical delivery
  - dermal
  - nasal
  - pulmonary



REGULATORY STATUS

FDA: The FDA has not challenged a self affirmed GRAS (Generally Recognized As Safe) status made by Eastman and approved products containing Vitamin E TPGS. It is registered as Inactive Ingredient under the name **Tocophersolan (UNII: O03S90U1F2)**.
USP : Monograph for Vitamin E TPGS is published in the current USP-NF.
CIR: Expert Panel (US): safe as **used in cosmetic** formulation.

Isochem owns a Type II DMF in the US for Vitamin E TPGS. Isochem's DMF includes impurity profile guaranty in addition to USP/NF.

ISOCHEM's DMF number: 23823

Samples for R&D work are available upon request

PACKAGING

Isochem Vitamin E TPGS is available in:

- 1 kg in glass bottle,
- 20 kg in polypropylene drum with full opening lid,
- 100 kg in epoxy coated steel drum with full opening lid and 2 stainless steel bungs, 3/4" and 2".

All packages are heat resistant up to 65°C which enables the customers to mobilise the product for handling. The total opening and bunds offer versatile options of drum emptying.

TRANSPORT

Material Safety Data Sheet disclosing safety precautions for handling and storage is available upon request.
Vitamin E TPGS is not classified as a dangerous good.

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TOXICOLOGY DATA

Oral LD-50	Higher than 7,000 mg/kg in rat (highest dose tested) Ref: Journal of Agricultural and Food Chemistry (1977), 25(2), 273-8
Skin LD-50	Higher than 2,000 mg/kg in rat (highest dose tested)
Skin Irritation	No effect
Eye Irritation	Slight effect
Skin Sensitization	None (guinea pig)

PHYSICAL AND CHEMICAL PROPERTIES

Chemical Abstract Index name:
α-[4-[[(2R)-3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-2H-1-benzopyran-6-yl]oxy]-1,4-dioxobutyl]-ω-hydroxy-poly(oxy-1,2-ethanediyl)

Empirical Formula: $C_{33}O_5H_{54}(CH_2CH_2O)_n$

Molecular Weight: 1513 (approx)

Physical form:
Vitamin E TPGS is water-soluble waxy solid with low melting point.

Color: White to light tan

Gardner Color:
Less than 10 (generally less than 5)

Vitamin E content (d-α-tocopherol):
25 % minimum weight basis; standard range 25-30 %

Potency UI/g: 428-446

Acid Value: 0.027 meq/g max

Reactivity:
Vitamin E TPGS reacts with alkali or nucleophiles, very low reactivity with air.

Stability of aqueous solution:
Data of stability solution at various pH will be available soon.

Specific Gravity: 1.06 at 50°C to 1.03 at 90°C

Melting Point: 38 °C (range 37-41)

Heat of melting: 99.8J/g

Heat capacity: 1.7 J/g.K

Solubility In Water:
~ 20% at 20°C
Forms gels between 20 to 90% mixture with water.

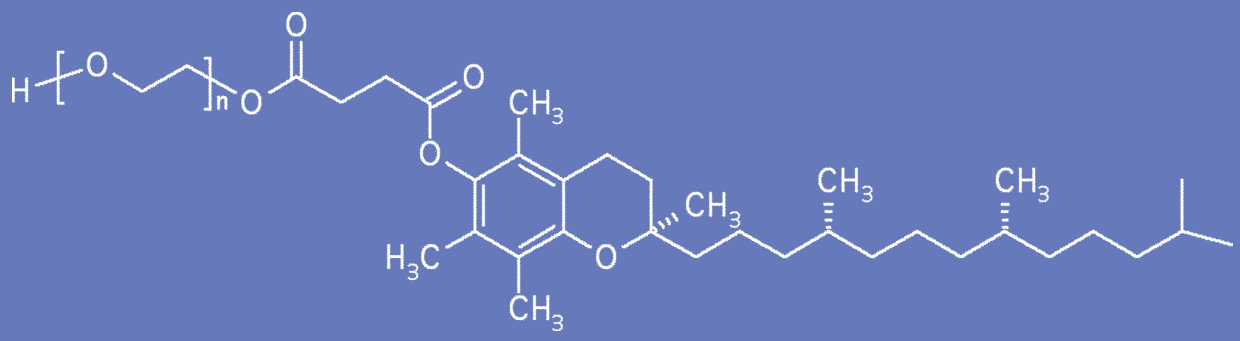
Specific Rotation [α]: Not less than + 24°

Viscosity: ~ 390cP at 50°C, (See Viscosity = f(T°C) scheme page 4).

Amphiphilic (Surface-Active) Properties:
Vitamin E TPGS has amphiphilic properties with a polar hydrophilic head (polyethylene glycol 1000) and a lipophilic tail (phytyl chain of d-α-tocopherol).

HLB (hydrophile/lipophile balance): 13

CMC (Critical Micelle Concentration):
0.02 weight % at 37°C. Vitamin E TPGS forms various liquid crystalline forms with water. Numerous micron level particle size diameter of liquid emulsions and solid formulations with TPGS are reported.

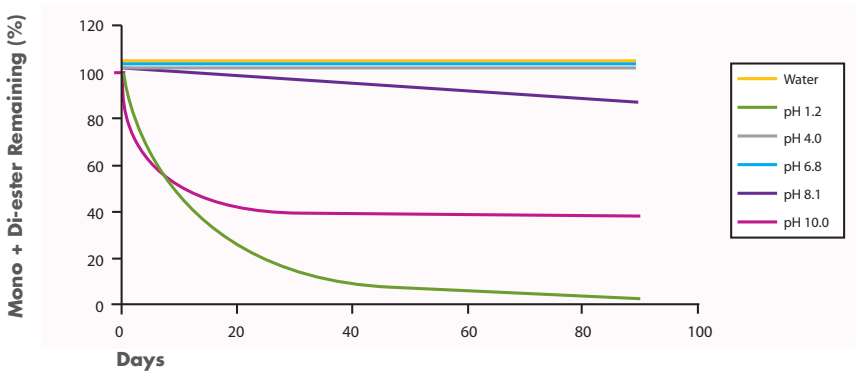


STABILITY

Vitamin E TPGS is a highly stable form of vitamin E. It is stable when exposed to oxygen, heat, light, or oxidizing agents. It is unstable to alkali. Vitamin E TPGS is known to be a stable excipient with a shelf-life of 4 years when stored in the original unopened container at room temperature. Vitamin E TPGS is stable under the conditions of heat sterilization.

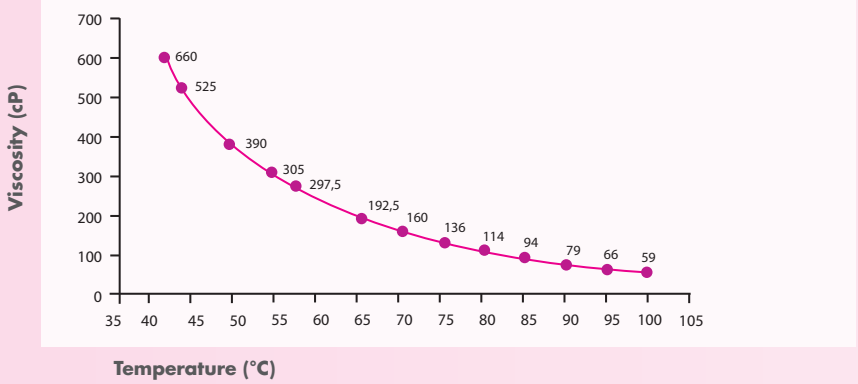
Thermal degradation temperature	No exotherm up to 300 °C
Oxydative thermal degradation	219°C
Stability under repetitive heat/cool/cycles	Stable 20 cycles (between 0 to 85°C)
Stability at 65°C	5 days
Flash Point	278°C
Sterilization	Stable when exposed to approximately 125 °C for 1 hour
Shelf-life	Isochem Vitamin E TPGS FG and NF grades are labelled with a 4 year shelf-life from the date of manufacturing when stored in the original sealed unopened container

Stability of vitamin E TPGS (10% aqueous solution at 37°C)



VISCOSITY

Viscosity values (cP) of Vitamin E TPGS



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REFERENCES
Further references are available on request

Safety studies references:

Monice Zondlo Fiume, Final Report on the Safety Assessment of Tocopherol, Tocopheryl Acetate, Tocopheryl Linoleate, Tocopheryl Linoleate/Oleate, Tocopheryl Nicotinate, Tocopheryl Succinate, Dioleyl Tocopheryl Methylsilanol, Potassium Ascorbyl Tocopheryl Phosphate, and Tocophersolan; *International Journal of Toxicology*, (2002), 21(Suppl. 3), 51-116.

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Bland,J. and Prestbo, E. Vitamin E : Comparative absorption studies, *International Clinical Nutrition review,* 1984, 4(2), 82-86.

Krasavage W.J., Terhaar C.J., d-alpha-Tocopheryl poly(ethylene glycol) 1000 succinate. Acute toxicity, subchronic feeding, reproduction, and teratologic studies in the rat *Journal of Agricultural and Food Chemistry*, (1977), 25(2), 273-8.

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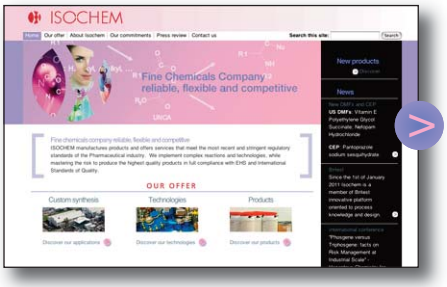

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Les Créations Philippe Tournire - Photos: Isochem

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