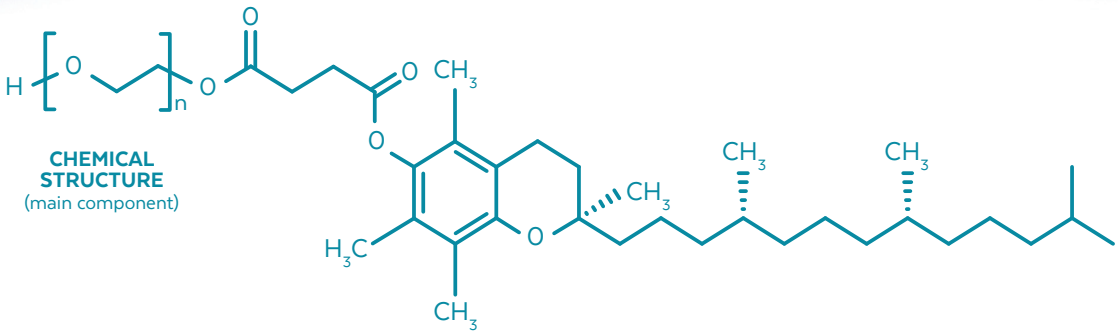
pmc isochem™

VITAMIN E TPGS

NF* and Food Grade

isodel®

CHEMICAL STRUCTURE
(main component)



CHEMICAL NAME
d-α tocopheryl polyethylene glycol 1000 succinate

SYNONYMS/ACRONYMS
Vitamin E TPGS or TPGS Tocofersolan
(INCI and USAN)** Tocofersolan

CAS REGISTRY NUMBER
9002-96-4

APPLICATION

PHARMACEUTICAL AND NUTRACEUTICAL
NUTRITIONAL SUPPLEMENTS
FOOD AND BEVERAGE
COSMETIC
PERSONAL CARE
ANIMAL NUTRITION

PMC Isochem Vitamin E TPGS is a versatile excipient used in pharmaceutical and nutraceutical applications. Vitamin E TPGS has proven properties to improve bioavailability of poorly soluble drugs, vitamins and micro-nutrients acting as a solubilizer, absorption and permeability enhancer.

Vitamin E TPGS is a functional ingredient of Self-Emulsifying Drug Delivery System (SEDDS) and a stabilizer of amorphous solid dispersion. Vitamin E TPGS is a plasticizer/binder for innovative technologies in the pharmaceutical industry such as hot melt extrusion .

Vitamin E TPGS is also used as an efficient source of natural Vitamin E, both for therapeutic purposes and nutrition.

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

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PMC Isochem:

- 10 YEARS OF GMP PRODUCTION AND SUPPLY FOR PHARMACEUTICAL DRUGS
- 2 PRODUCTION PLANTS (> 100T capacity)
- YOUR PARTNER FOR YOUR INNOVATION AND REGULATORY APPROVAL

PMC 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.

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

PMC Isochem Vitamin E TPGS is manufactured in France in state of the art FDA audited cGMP facilities. PMC 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).

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

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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VITAMIN E TPGS PROPERTIES

DRUG BIOAVAILABILITY

- Solubilizer of poorly water soluble drugs
- Enhancer of drug permeability by P-glycoprotein efflux inhibition
- Stabilizer of amorphous drug dispersion

FUNCTIONAL INGREDIENT

- Ingredient self-emulsifying formulations
- Thermal binder in melt granulation/extrusion processing

WATER SOLUBLE SOURCE OF VITAMIN E

DOSAGE FORMS

- Oral
- Parenteral
- Topical

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.

PMC Isochem owns a Type II DMF in the US for Vitamin E TPGS.

PMC Isochem's DMF includes impurity profile guaranty in addition to USP/NF.

PMC ISOCHEM'S DMF number: 23823

PACKAGING

PMC Isochem VITAMIN E TPGS IS AVAILABLE IN:

- 20 kg in polyethylene 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. For R&D purpose, 1 kg in polyethylene box is available upon request.

Samples for R&D work
are available upon request

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.

HANDLING

Standard operating condition for melting, emptying drums and handling liquid TPGS is available upon request.

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.

PMC ISOCHEM's DMF number: 23823

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).

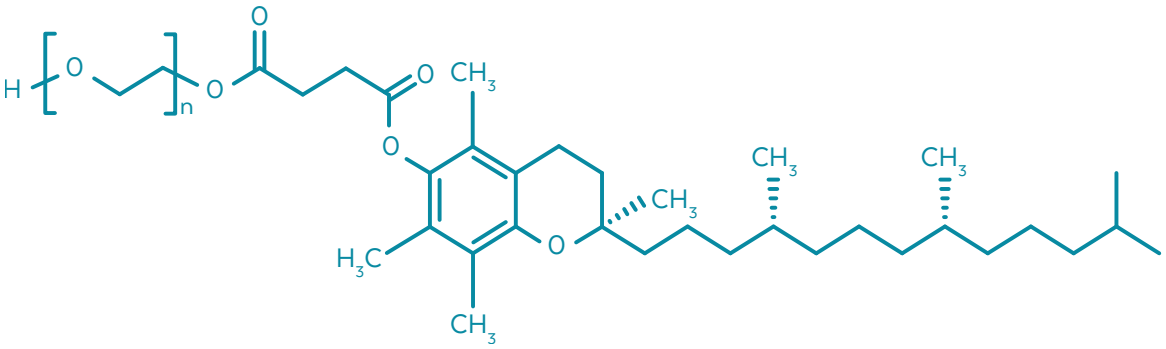
Amphiphilic (Surface-Active) Properties:

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.

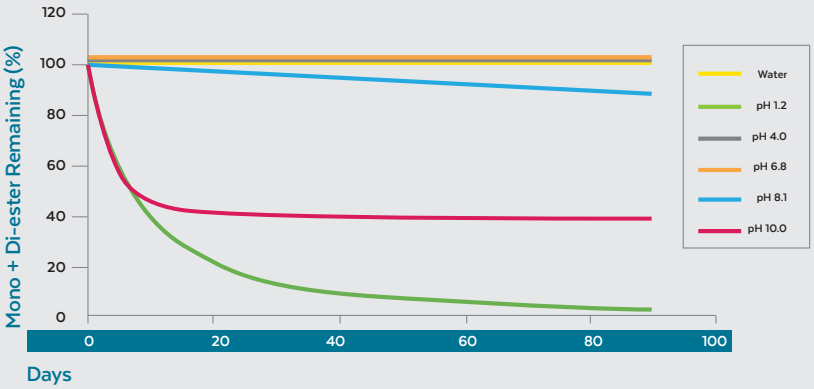


STABILITY

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 A STABLE EXCIPIENT WITH A SHELF-LIFE OF 4 YEARS WHEN STORED IN THE ORIGINAL UNOPENED CONTAINER AT ROOM TEMPERATURE. (STATEMENT AVAILABLE UPON REQUEST)

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



Thermal degradation temperature
NO EXOTHERM UP TO
300°C

Oxydative thermal degradation
219°C

Flash Point
278°C

Sterilization
STABLE WHEN EXPOSED TO APPROXIMATELY
125°C
FOR 1 HOUR

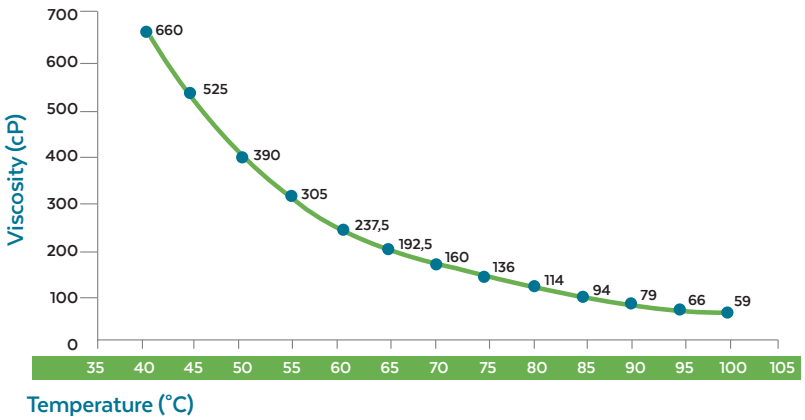
Stability under repetitive heat/ cool/ cycles (Differential scanning calorimetry)
STABLE
20 CYCLES
(BETWEEN 0 TO 85°C)

ICH stability study
48 MONTHS AT
25°C
6 MONTHS AT
40°C

Stability in commercial packaging after 5 cycles heat at 60°C /cool at 20°C
CONFORM TO THE SPECIFICATION

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.

National Cancer Institute, "One-Year Chronic Oral (Intubation) Study In Dogs and Rats", (National Institute of health, Bethesda M. D., 1994).

Friman, S., Leandersson, P., Tagesson, C., and Svanvik, J. Biliary Excretion of Different Sized Polyethylene Glycols in the Cat. J Hepatology, 1990, 11: 215-220.

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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