

---

**Handbook of  
PHARMACEUTICAL  
EXCIPIENTS**

---

**Second Edition**

*Edited by*  
**Ainley Wade and Paul J Weller**

American Pharmaceutical Association  
Washington

The Pharmaceutical Press  
London

1994

© Copyright 1986, 1994 by the American Pharmaceutical Association, 2215 Constitution Avenue NW, Washington, DC 20037-2985, USA, and The Pharmaceutical Press, Royal Pharmaceutical Society of Great Britain, 1 Lambeth High Street, London, SE1 7JN, England.

A catalogue record for this book is available from the British Library.

Library of Congress Catalog Card Number: 94-79492.

International Standard Book Number (ISBN) in the UK: 0 85369 305 6  
International Standard Book Number (ISBN) in the USA: 0 91730 66 8

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage or retrieval system, without prior written permission from the joint publishers.

Typeset in Great Britain by Alden Multimedia, Northampton.  
Printed and bound in Great Britain by

# Contents

Committees	vii	Croscarmellose Sodium	141
Contributors	viii	Crospovidone	143
Additions to the Second Edition	ix	Cyclodextrins	145
Preface	xi	Dextrates	149
Notice to Readers	xiii	Dextrin	151
Selected Bibliography	xiii	Dextrose	154
Abbreviations	xiv	Dibutyl Sebacate	158
Units of Measurement	xv	Dichlorodifluoromethane	160
		Dichlorotetrafluoroethane	163
		Diethanolamine	165
		Diethyl Phthalate	167
		Difluoroethane	169
		Dimethyl Ether	171
		Docusate Sodium	173
		Edetic Acid	176
		Ethyl Maltol	180
		Ethyl Oleate	182
		Ethyl Vanillin	184
		Ethylcellulose	186
		Ethylparaben	191
		Fructose	194
		Fumaric Acid	197
		Gelatin	199
		Liquid Glucose	202
		Glycerin	204
		Glyceryl Monooleate	207
		Glyceryl Monostearate	209
		Glyceryl Palmitostearate	211
		Glycofurof	213
		Guar Gum	215
		Hydrochloric Acid	217
		Hydroxyethyl Cellulose	219
		Hydroxypropyl Cellulose	223
		Hydroxypropyl Methylcellulose	229
		Hydroxypropyl Methylcellulose Phthalate	233
		Imidurea	238
		Isobutane	240
		Isopropyl Alcohol	241
		Isopropyl Myristate	243
		Isopropyl Palmitate	245
		Kaolin	247
		Lactic Acid	250
		Lactose	252
		Lanolin	262
		Lanolin Alcohols	264
		Hydrous Lanolin	265
		Lecithin	267
		Magnesium Aluminum Silicate	269
		Magnesium Carbonate	274
		Magnesium Oxide	278
		Magnesium Stearate	280
		Magnesium Trisilicate	283
		Malic Acid	285
		Maltitol Solution	287
		Maltodextrin	289
		Maltol	292
		Mannitol	294
		Medium Chain Triglycerides	299
		Meglumine	302
		Menthol	304
		Methylcellulose	306
		Methylparaben	310
		Mineral Oil	314
		Light Mineral Oil	316
		Mineral Oil and Lanolin Alcohols	318
		Monoethanolamine	319
<b>Monographs</b>			
Acacia	1		
Acesulfame Potassium	3		
Albumin	5		
Alcohol	7		
Alginic Acid	10		
Alpha Tocopherol	12		
Ascorbic Acid	15		
Ascorbyl Palmitate	19		
Aspartame	21		
Bentonite	24		
Benzalkonium Chloride	27		
Benzethonium Chloride	30		
Benzoic Acid	32		
Benzyl Alcohol	35		
Benzyl Benzoate	38		
Bronopol	40		
Butane	43		
Butylated Hydroxyanisole	45		
Butylated Hydroxytoluene	47		
Butylparaben	49		
Calcium Carbonate	52		
Dibasic Calcium Phosphate Dihydrate	56		
Tribasic Calcium Phosphate	61		
Calcium Stearate	63		
Calcium Sulfate	66		
Canola Oil	69		
Carbomer	71		
Carbon Dioxide	74		
Carboxymethylcellulose Calcium	76		
Carboxymethylcellulose Sodium	78		
Hydrogenated Castor Oil	82		
Microcrystalline Cellulose	84		
Powdered Cellulose	88		
Cellulose Acetate Phthalate	91		
Cetostearyl Alcohol	94		
Cetrimide	96		
Cetyl Alcohol	99		
Cetyl Esters Wax	104		
Chlorhexidine	106		
Chlorobutanol	111		
Chlorocresol	114		
Chlorodifluoroethane	117		
Chlorodifluoromethane	119		
Cholesterol	121		
Citric Acid Monohydrate	123		
Coloring Agents	126		
Corn Oil	135		
Cottonseed Oil	137		
Cresol	139		

Nitrogen	321	Dibasic Sodium Phosphate	454
Nitrous Oxide	323	Monobasic Sodium Phosphate	457
Oleic Acid	325	Sodium Propionate	459
Paraffin	327	Sodium Starch Glycolate	462
Peanut Oil	329	Sodium Stearyl Fumarate	467
Petrolatum	331	Sorbic Acid	470
Petrolatum and Lanolin Alcohols	334	Sorbitan Esters (Sorbitan Fatty Acid Esters)	473
Phenol	336	Sorbitol	477
Phenoxyethanol	338	Soybean Oil	481
Phenylethyl Alcohol	340	Starch	483
Phenylmercuric Acetate	342	Sterilizable Maize Starch	489
Phenylmercuric Borate	344	Pregelatinized Starch	491
Phenylmercuric Nitrate	346	Stearic Acid	494
Polacrilin Potassium	350	Stearyl Alcohol	498
Poloxamer	352	Sucrose	500
Polyethylene Glycol	355	Compressible Sugar	506
Polymethacrylates	362	Confectioner's Sugar	508
Polyoxyethylene Alkyl Ethers	367	Sugar Spheres	510
Polyoxyethylene Castor Oil Derivatives	371	Suppository Bases	512
Polyoxyethylene Sorbitan Fatty Acid Esters	375	Talc	519
Polyoxyethylene Stearates	379	Tartaric Acid	522
Polyvinyl Alcohol	383	Tetrafluoroethane	524
Potassium Chloride	385	Thimerosal	526
Potassium Citrate	388	Titanium Dioxide	529
Potassium Sorbate	390	Tragacanth	532
Povidone	392	Triacetin	534
Propane	400	Trichloromonofluoromethane	536
Propyl Gallate	402	Triethanolamine	538
Propylene Carbonate	405	Triethyl Citrate	540
Propylene Glycol	407	Vanillin	542
Propylene Glycol Alginate	409	Hydrogenated Vegetable Oil, Type I	544
Propylparaben	411	Water	546
Saccharin	415	Anionic Emulsifying Wax	550
Saccharin Sodium	418	Carnauba Wax	552
Sesame Oil	420	Microcrystalline Wax	554
Shellac	422	Nonionic Emulsifying Wax	556
Colloidal Silicon Dioxide	424	White Wax	558
Sodium Alginate	428	Yellow Wax	560
Sodium Ascorbate	431	Xanthan Gum	562
Sodium Benzoate	433	Xylitol	564
Sodium Bicarbonate	436	Zein	568
Sodium Chloride	439	Zinc Stearate	569
Sodium Citrate Dihydrate	443	<i>Appendix I: Suppliers' Directory</i>	571
Sodium Cyclamate	446	<i>Appendix II: HPE Laboratory Methods</i>	625
Sodium Lauryl Sulfate	448	<i>Index</i>	633
Sodium Metabisulfite	451		

# Alpha Tocopherol

## 1. Nonproprietary Names

BP: Alpha tocopherol  
PhEur:  $\alpha$ -Tocopherolum  
USP: Vitamin E  
See also Sections 3, 9 and 18.

## 2. Synonyms

( $\pm$ )-3,4-Dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-ol; E307; synthetic alpha tocopherol; *all-rac*- $\alpha$ -tocopherol; *dl*- $\alpha$ -tocopherol; 5,7,8-trimethyltolcol.

## 3. Chemical Name and CAS Registry Number

( $\pm$ )-(2*RS*,4'*RS*,8'*RS*)-2,5,7,8-Tetramethyl-2-(4',8',12'-trimethyltridecyl)-6-chromanol  
[10191-41-0]

Note that alpha tocopherol has three chiral centres giving rise to eight isomeric forms. The naturally occurring form is known as *d*-alpha tocopherol or (2*R*,4'*R*,8'*R*)-alpha-tocopherol. The synthetic form, *dl*-alpha tocopherol or simply alpha tocopherol, occurs as a racemic mixture containing equimolar quantities of all the isomers.

Similar considerations apply to beta, delta and gamma tocopherol and tocopherol esters.

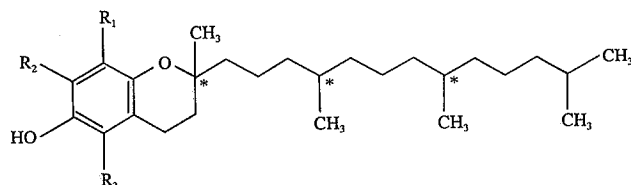
See Section 18 for further information.

## 4. Empirical Formula      Molecular Weight

C<sub>29</sub>H<sub>50</sub>O<sub>2</sub>

430.69

## 5. Structural Formula



Alpha tocopherol: R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = CH<sub>3</sub>.

Beta tocopherol: R<sub>1</sub> = R<sub>3</sub> = CH<sub>3</sub>; R<sub>2</sub> = H.

Delta tocopherol: R<sub>1</sub> = CH<sub>3</sub>; R<sub>2</sub> = R<sub>3</sub> = H.

Gamma tocopherol: R<sub>1</sub> = R<sub>2</sub> = CH<sub>3</sub>; R<sub>3</sub> = H.

\* Indicates chiral centres.

## 6. Functional Category

Antioxidant; therapeutic agent.

## 7. Applications in Pharmaceutical Formulation or Technology

Alpha tocopherol is primarily recognised as a source of vitamin E and the commercially available materials and specifications reflect this purpose. Whilst alpha tocopherol also exhibits antioxidant properties, the beta, delta and gamma tocopherols are considered to be more effective as antioxidants.

Of widespread regulatory acceptability, tocopherols are of value in oil or fat-based pharmaceutical products and are normally used in the concentration range of 0.001-0.05%.

There is frequently an optimum concentration; thus the autoxidation of linoleic acid and methyl linolenate is reduced at low concentrations of alpha tocopherol but accelerated by higher concentrations. Antioxidant effectiveness can be increased by the addition of oil soluble synergists such as lecithin and ascorbyl palmitate.<sup>(1)</sup>

## 8. Description

Alpha tocopherol is a practically odorless, clear, colorless, yellow, yellowish-brown or greenish-yellow colored viscous oil. See also Section 18.

## 9. Pharmacopeial Specifications

Test	PhEur 1990	USP XXII
Identification	+	+
Acidity	—	+
Acid value	≤ 2	—
Heavy metals	≤ 20 ppm	—
Sulfated ash	≤ 0.1%	—
Assay	96.0-102.0%	96.0-102.0%

Note that the USP XXII describes vitamin E as comprising *d*- or *dl*-alpha tocopherol; *d*- or *dl*-alpha tocopheryl acetate; or *d*- or *dl*-alpha tocopheryl acid succinate. However, the PhEur 1990 and the BP 1993 describe alpha tocopherol and alpha tocopheryl acetate in separate monographs.

The diversity of the tocopherols described in the various pharmacopeial monographs makes a comparison of specifications difficult.

## 10. Typical Properties

*Solubility*: practically insoluble in water; freely soluble in acetone, ethanol, ether and vegetable oils.

## 11. Stability and Storage Conditions

Tocopherols are slowly oxidized by atmospheric oxygen and rapidly by ferric and silver salts. Oxidation products include tocopheroxide, tocopherylquinone and tocopherylhydroquinone, as well as dimers and trimers. Tocopherol esters are more stable to oxidation than the free tocopherols but are in consequence less effective antioxidants. See also Section 18.

Tocopherols should be stored under an inert gas, in an airtight container in a cool, dry, place and protected from light.

## 12. Incompatibilities

Tocopherols are incompatible with peroxides and metal ions especially iron, copper and silver. Tocopherols may be absorbed into plastic.<sup>(2)</sup>

## 13. Method of Manufacture

Naturally occurring tocopherols are obtained by the extraction or molecular distillation of steam distillates of vegetable oils, e.g. alpha tocopherol occurs in concentrations of 0.1-0.3% in corn, rapeseed, soybean, sunflower and wheat germ oils.<sup>(3)</sup>

Beta tocopherol and gamma tocopherol are usually found in natural sources along with alpha tocopherol. Racemic synthetic tocopherols may be prepared by the condensation of the appropriate methylated hydroquinone with racemic isophytol.<sup>(4)</sup>

## 14. Safety

Tocopherols (vitamin E) occur in many food substances that are consumed as part of the normal diet. The daily nutritional

Noven Ex 1003

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.