

HANDBOOK OF
PHARMACEUTICAL
EXCIPIENTS

THIRD EDITION



APhA
American
Pharmaceutical
Association



EDITED BY
ARTHUR H. KIBBE

Handbook of PHARMACEUTICAL EXCIPIENTS

Third Edition

Edited by

Arthur H. Kibbe, Ph.D.

Professor and Chair
Department of Pharmaceutical Sciences
Wilkes University School of Pharmacy
Wilkes-Barre, Pennsylvania



American Pharmaceutical Association
Washington, D.C.



London, United Kingdom

Published by the American Pharmaceutical Association
2215 Constitution Avenue NW, Washington, DC 20037-2985, USA
www.aphanet.org
and the Pharmaceutical Press
1 Lambeth High Street, London SE1 7JN, UK
www.pharmpress.com

© 1986, 1994, 2000 American Pharmaceutical Association and Pharmaceutical Press

First edition 1986
Second edition 1994
Third edition 2000

Printed in the United States of America

ISBN: 0-85369-381-1 (UK)
ISBN: 0-917330-96-X (USA)

Library of Congress Cataloging-in-Publication Data

Handbook of pharmaceutical excipients / edited by Arthur H. Kibbe.--3rd ed.
p. ; cm.

Includes bibliographical references and index.

ISBN 0-917330-96-X

1. Excipients--Handbooks, manuals, etc. I. Kibbe, Arthur H. II. American Pharmaceutical Association.

[DNLM: 1. Excipients--Handbooks. QV 735 H236 2000]

RS201.E87 H36 2000

615'.19--dc21

99-044554

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

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, without the prior written permission of the copyright holder. The publisher makes no representation, express or implied, with regard to the accuracy of the information contained in this book and cannot accept any legal responsibility or liability for any errors or omissions that may be made.

Managing Editor: Melanie Segala
Copyeditor: Paul Gottehrer
Indexer: Lillian Rodberg
Compositor: Roy Barnhill
Cover Designer: Tim Kaage

Ethylparaben

1. Nonproprietary Names

BP: Ethyl hydroxybenzoate
 JP: Ethyl parahydroxybenzoate
 PhEur: Ethylis parahydroxybenzoas
 USP: Ethylparaben

2. Synonyms

Cosept E; E214; ethyl *p*-hydroxybenzoate; *Ethyl parasept*; 4-hydroxybenzoic acid ethyl ester; *Nipagin A*; *Preserval E*; *Solbrol A*; *Tegosept E*; *Unisept E*.

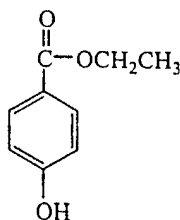
3. Chemical Name and CAS Registry Number

Ethyl 4-hydroxybenzoate [120-47-8]

4. Empirical Formula Molecular Weight

$C_9H_{10}O_3$ 166.18

5. Structural Formula



6. Functional Category

Antimicrobial preservative.

7. Applications in Pharmaceutical Formulation or Technology

Ethylparaben is widely used as an antimicrobial preservative in cosmetics, food products, and pharmaceutical formulations. It may be used either alone, in combination with other paraben esters, or with other antimicrobial agents. In cosmetics it is the sixth most frequently used preservative.⁽¹⁾

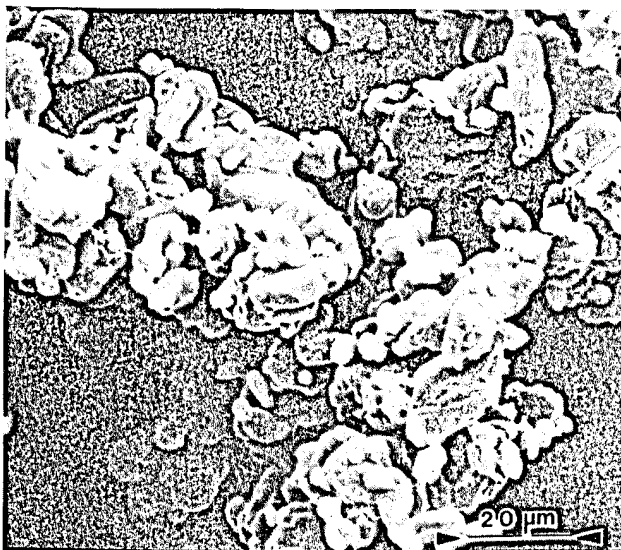
The parabens are effective over a wide pH range and have a broad spectrum of antimicrobial activity although they are most effective against yeasts and molds, *see* Section 10.

Due to the poor solubility of the parabens, paraben salts, particularly the sodium salt, are frequently used. However, this may cause the pH of poorly buffered formulations to become more alkaline.

See Methylparaben for further information.

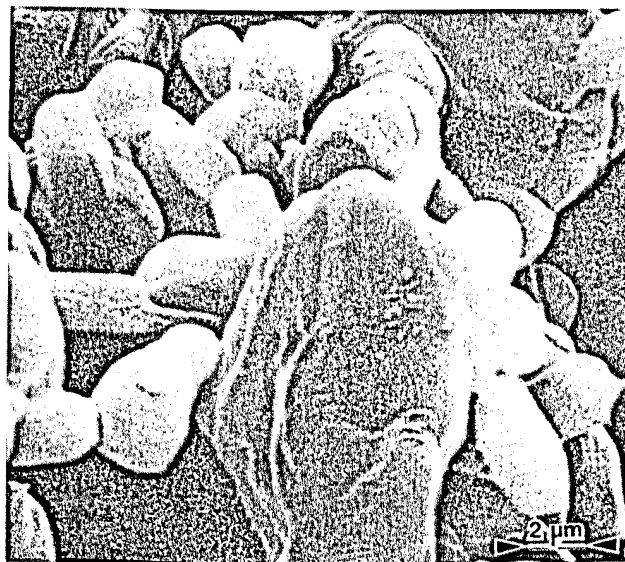
SEM: 1

Excipient: Ethylparaben
 Magnification: 600×



SEM: 2

Excipient: Ethylparaben
 Magnification: 3000×



8. Description

Ethylparaben occurs as a white-colored, odorless or almost odorless, crystalline powder.

9. Pharmacopeial Specifications

Test	JP	PhEur	USP
Identification	+	+	+
Characters	+	+	—
Appearance of solution	—	+	—
Melting range	116-118°C	115-118°C	115-118°C
Acidity	—	+	+
Loss on drying	≤ 0.5%	—	≤ 0.5%
Residue on ignition	≤ 0.1%	—	≤ 0.05%
Sulfated ash	—	≤ 0.1%	—
Chloride	≤ 0.035%	—	—
Sulfate	≤ 0.024%	—	—
Heavy metals	≤ 20 ppm	—	—
Readily carbonizable substances	+	—	—
Related substances	+	+	—
Organic volatile impurities	—	—	+
Assay (dried basis)	≥ 99.0%	99.0-101.0%	99.0-100.5%

10. Typical Properties

Antimicrobial activity: ethylparaben exhibits antimicrobial activity between pH 4-8. Preservative efficacy decreases with increasing pH due to the formation of the phenolate anion. Parabens are more active against yeasts and molds than against bacteria. They are also more active against Gram-positive than against Gram-negative bacteria.

The activity of the parabens increases with increasing chain length of the alkyl moiety; solubility however decreases. Activity may be improved by using combinations of parabens since additive effects occur. Ethylparaben is thus commonly used with methyl and propylparaben in oral and topical formulations. (Such mixtures are commercially available, e.g., *Nipasept* (Nipa Laboratories Inc.)). Activity has also been reported to be improved by the addition of other excipients, *see* Methylparaben for further information.

Reported minimum inhibitory concentrations (MICs) for ethylparaben are shown in Table I.⁽²⁾

Boiling point: 297-298°C with decomposition

Melting point: 115-118°C

Partition coefficients: values for different vegetable oils vary considerably and are affected by the purity of the oil, *see* Table II.

Solubility: *see* Table III.

11. Stability and Storage Conditions

Aqueous ethylparaben solutions at pH 3-6 can be sterilized by autoclaving without decomposition.⁽⁴⁾ At pH 3-6 aqueous solutions are stable (less than 10% decomposition) for up to about 4 years at room temperature while solutions at pH 8 or above are subject to rapid hydrolysis (10% or more after about 60 days at room temperature).⁽⁵⁾

Ethylparaben should be stored in a well-closed container in a cool, dry, place.

12. Incompatibilities

The antimicrobial properties of ethylparaben are considerably reduced in the presence of nonionic surfactants as a result of micellization.⁽⁶⁾ Absorption of ethylparaben by plastics has not been reported and appears probable given the behavior of other para-

Table I: Minimum inhibitory concentrations (MICs) for ethylparaben in aqueous solution.⁽²⁾

Microorganism	MIC (µg/mL)
<i>Aerobacter aerogenes</i> ATCC 8308	1200
<i>Aspergillus niger</i> ATCC 9642	500
<i>Aspergillus niger</i> ATCC 10254	400
<i>Bacillus cereus var. mycoides</i> ATCC 6462	1000
<i>Bacillus subtilis</i> ATCC 6633	1000
<i>Candida albicans</i> ATCC 10231	500
<i>Enterobacter cloacae</i> ATCC 23355	1000
<i>Escherichia coli</i> ATCC 8739	1000
<i>Escherichia coli</i> ATCC 9637	1000
<i>Klebsiella pneumoniae</i> ATCC 8308	500
<i>Penicillium chrysogenum</i> ATCC 9480	250
<i>Penicillium digitatum</i> ATCC 10030	250
<i>Proteus vulgaris</i> ATCC 13315	500
<i>Pseudomonas aeruginosa</i> ATCC 9027	> 2000
<i>Pseudomonas aeruginosa</i> ATCC 15442	> 2000
<i>Pseudomonas stutzeri</i>	1000
<i>Rhizopus nigricans</i> ATCC 6227A	250
<i>Saccharomyces cerevisiae</i> ATCC 9763	500
<i>Salmonella typhosa</i> ATCC 6539	1000
<i>Serratia marcescens</i> ATCC 8100	1000
<i>Staphylococcus aureus</i> ATCC 6538P	1000
<i>Staphylococcus epidermidis</i> ATCC 12228	1000
<i>Trichophyton mentagrophytes</i>	125

Table II: Partition coefficients for ethylparaben in vegetable oil and water.⁽³⁾

Solvent	Partition coefficient Oil: water
Corn oil	14.0
Mineral oil	0.13
Peanut oil	16.1
Soybean oil	18.8

Table III: Solubility of ethylparaben in various solvents.⁽²⁾

Solvent	Solubility at 25°C Unless otherwise stated
Acetone	Freely soluble
Ethanol	1 in 1.4
Ethanol (95%)	1 in 2
Ether	1 in 3.5
Glycerin	1 in 200
Methanol	1 in 0.9
Mineral oil	1 in 4000
Peanut oil	1 in 100
Propylene glycol	1 in 4
Water	1 in 1250 at 15°C 1 in 910 at 20°C

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.