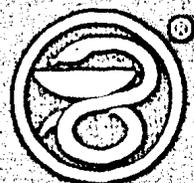


HANDBOOK OF
PHARMACEUTICAL

EXCIPIENTS

THIRD EDITION



APhA
American
Pharmaceutical
Association



EDITED BY
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Handbook of PHARMACEUTICAL EXCIPIENTS

Third Edition

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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*.

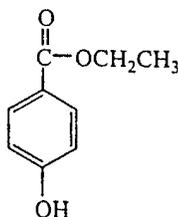
3. Chemical Name and CAS Registry Number

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⁾

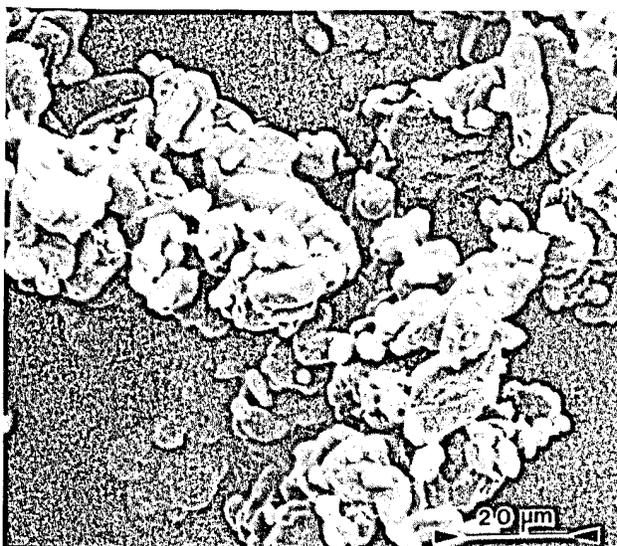
The parabens are effective over a wide pH range and have a broad spectrum of antimicrobial activity although they are most effective against yeasts and molds, *see* Section 10.

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.

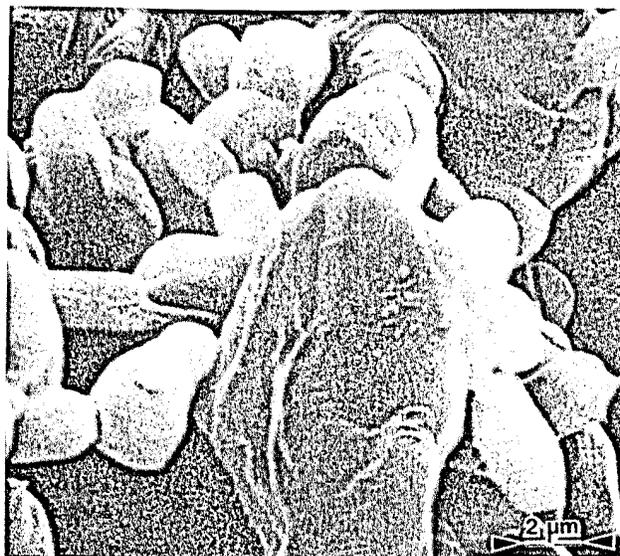
SEM: 1

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</i> var. <i>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 |

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