HANDBOOK OF PHARMACEUTICAL EXCIPIENTS

THIRD EDITION

EDITED BY

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Methylparaben

1. Nonproprietary Names

BP: Methyl hydroxybenzoate
JP: Methyl parahydroxybenzoate
PhEur: Methylis parahydroxybenzoas
USP: Methylparaben

2. Synonyms

E218; 4-hydroxybenzoic acid methyl ester; *Methyl Chemosept*; methyl *p*-hydroxybenzoate; *Methyl Parasept*; *Nipagin M*; *Solbrol M*; *Tegosept M*.

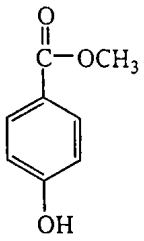
3. Chemical Name and CAS Registry Number

Methyl 4-hydroxybenzoate [99-76-3]

4. Empirical Formula and Molecular Weight

Empirical Formula	Molecular Weight
$C_8H_8O_3$	152.15

5. Structural Formula



6. Functional Category

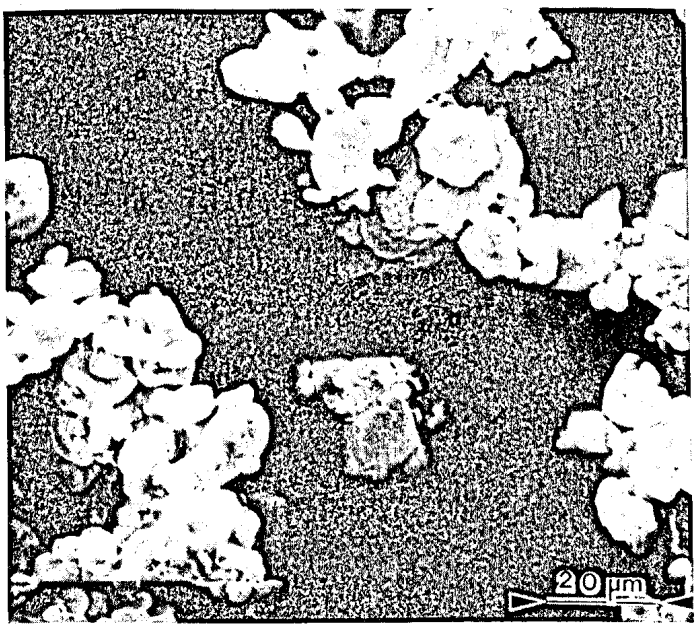
Antimicrobial preservative.

7. Applications in Pharmaceutical Formulation or Technology

Methylparaben is widely used as an antimicrobial preservative in cosmetics, food products, and pharmaceutical formulations. It may be used either alone, in combination with other parabens, or with other antimicrobial agents. In cosmetics, methylparaben is the most frequently used antimicrobial 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. Antimicrobial activity increases as the chain length of the alkyl moiety is increased; aqueous solubility however decreases. A mixture of parabens is thus frequently used to provide effective preservation. Preservative efficacy is also improved by the addition of 2-5% propylene glycol, or by using parabens in combination with other antimicrobial agents such as imidurea, *see* Section 10.

SEM: 1
Excipient: Methylparaben
Supplier: Bate Chemical Co Ltd
Magnification: 600×



Methylparaben (0.18%) together with propylparaben (0.02%) has been used for the preservation of various parenteral pharmaceutical formulations, *see* Section 14.

Use	Concentration (%)
IM, IV, SC injections[a]	0.065-0.25
Inhalation solutions	0.025-0.07
Intradermal injections	0.10
Nasal solutions	0.033
Ophthalmic preparations[a]	0.015-0.2
Oral solutions and suspensions	0.015-0.2
Rectal preparations	0.1-0.18
Topical preparations	0.02-0.3
Vaginal preparations	0.1-0.18

[a] *See* Section 14.

8. Description

Methylparaben occurs as colorless crystals or a white crystalline powder. It is odorless or almost odorless and has a slight burning taste.

9. Pharmacopeial Specifications

Test	JP	PhEur	USP
Identification	+	+	+
Characters	+	+	—
Melting range	125-128°C	125-128°C	125-128°C
Acidity	—	+	+
Loss on drying	≤ 0.5%	—	≤ 0.5%
Residue on ignition	≤ 0.10%	—	≤ 0.05%

(Continued)

Test	JP	PhEur	USP
Sulfate	≤ 0.024%	—	—
Heavy metals	≤ 20 ppm	—	—
Readily carbonizable substances	+	—	—
Appearance of solution	—	+	+
Related substances	+	+	—
Assay (dried basis)	≥ 99.0%	99.0-100.5%	99.0-100.5%

10. Typical Properties

Antimicrobial activity: methylparaben 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 bacteria than against Gram-negative bacteria.

Methylparaben is the least active of the parabens; antimicrobial activity increases with increasing chain length of the alkyl moiety. Activity may be improved by using combinations of parabens, since additive effects occur. Therefore, combinations of methyl, ethyl, propyl, and butylparaben are often used together. Activity has also been reported to be enhanced by the addition of other excipients such as: propylene glycol (2-5%);[2] phenylethyl alcohol;[3] and edetic acid.[4] Activity may also be enhanced, due to synergistic effects, by using combinations of parabens with other antimicrobial preservatives such as imidurea.[5]

The hydrolysis product, *p*-hydroxybenzoic acid, has practically no antimicrobial activity.

See also Section 12.

Reported minimum inhibitory concentrations (MICs) for methylparaben are shown in Table I.[4]

Density (true): 1.352 g/cm^3[a]

Dissociation constant: pK_a = 8.4 at 22°C

Melting point: 125-128°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

[a] Results of laboratory project for third edition.

11. Stability and Storage Conditions

Aqueous solutions of methylparaben, at pH 3-6, may be sterilized by autoclaving at 120°C for 20 minutes, without decomposition.[8] Aqueous solutions at pH 3-6 are stable (less than 10% decomposition) for up to about 4 years at room temperature, while aqueous solutions at pH 8 or above are subject to rapid hydrolysis (10% or more after about 60 days storage at room temperature).[9]

Predicted rate constants and half-lives at 25°C, for methylparaben dissolved in dilute hydrochloric acid solution at the initial pH shown below:[9]

Initial pH of solution	Rate constant $k \pm \sigma$[a] (hour^{-1})	Half-life $t_{½} \pm \sigma$[a] (day)
1	$(1.086 \pm 0.005) \times 10^{-4}$	266 ± 13
2	$(1.16 \pm 0.12) \times 10^{-5}$	2490 ± 260
3	$(6.1 \pm 1.5) \times 10^{-7}$	47000 ± 12000

Table I: Minimum inhibitory concentrations (MICs) of methylparaben in aqueous solution.[4]

Microorganism	MIC (µg/mL)
Aerobacter aerogenes ATCC 8308	2000
Aspergillus oryzae	600
Aspergillus niger ATCC 9642	1000
Aspergillus niger ATCC 10254	1000
Bacillus cereus var. mycoides ATCC 6462	2000
Bacillus subtilis ATCC 6633	2000
Candida albicans ATCC 10231	2000
Enterobacter cloacae ATCC 23355	1000
Escherichia coli ATCC 8739	1000
Escherichia coli ATCC 9637	1000
Klebsiella pneumoniae ATCC 8308	1000
Penicillium chrysogenum ATCC 9480	500
Penicillium digitatum ATCC 10030	500
Proteus vulgaris ATCC 8427	2000
Proteus vulgaris ATCC 13315	1000
Pseudomonas aeruginosa ATCC 9027	4000
Pseudomonas aeruginosa ATCC 15442	4000
Pseudomonas stutzeri	2000
Rhizopus nigricans ATCC 6227A	500
Saccharomyces cerevisiae ATCC 9763	1000
Salmonella typhosa ATCC 6539	1000
Sarcina lutea	4000
Serratia marcescens ATCC 8100	1000
Staphylococcus aureus ATCC 6538P	2000
Staphylococcus epidermidis ATCC 12228	2000
Trichoderma lignorum ATCC 8678	250
Trichoderma mentagrophytes	250

Table II: Partition coefficients of methylparaben in vegetable oil and water.[6,7]

Solvent	Partition coefficient Oil: water
Almond oil	7.5
Castor oil	6.0
Corn oil	4.1
Diethyl adipate	200
Isopropyl myristate	18.0
Lanolin	7.0
Mineral oil	0.1
Peanut oil	4.2
Soybean oil	6.1

Table III: Solubility of methylparaben in various solvents.[4]

Solvent	Solubility at 25°C Unless otherwise stated
Ethanol	1 in 2
Ethanol (95%)	1 in 3
Ethanol (50%)	1 in 6
Ether	1 in 10
Glycerin	1 in 60
Mineral oil	Practically insoluble
Peanut oil	1 in 200
Propylene glycol	1 in 5
Water	1 in 400

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