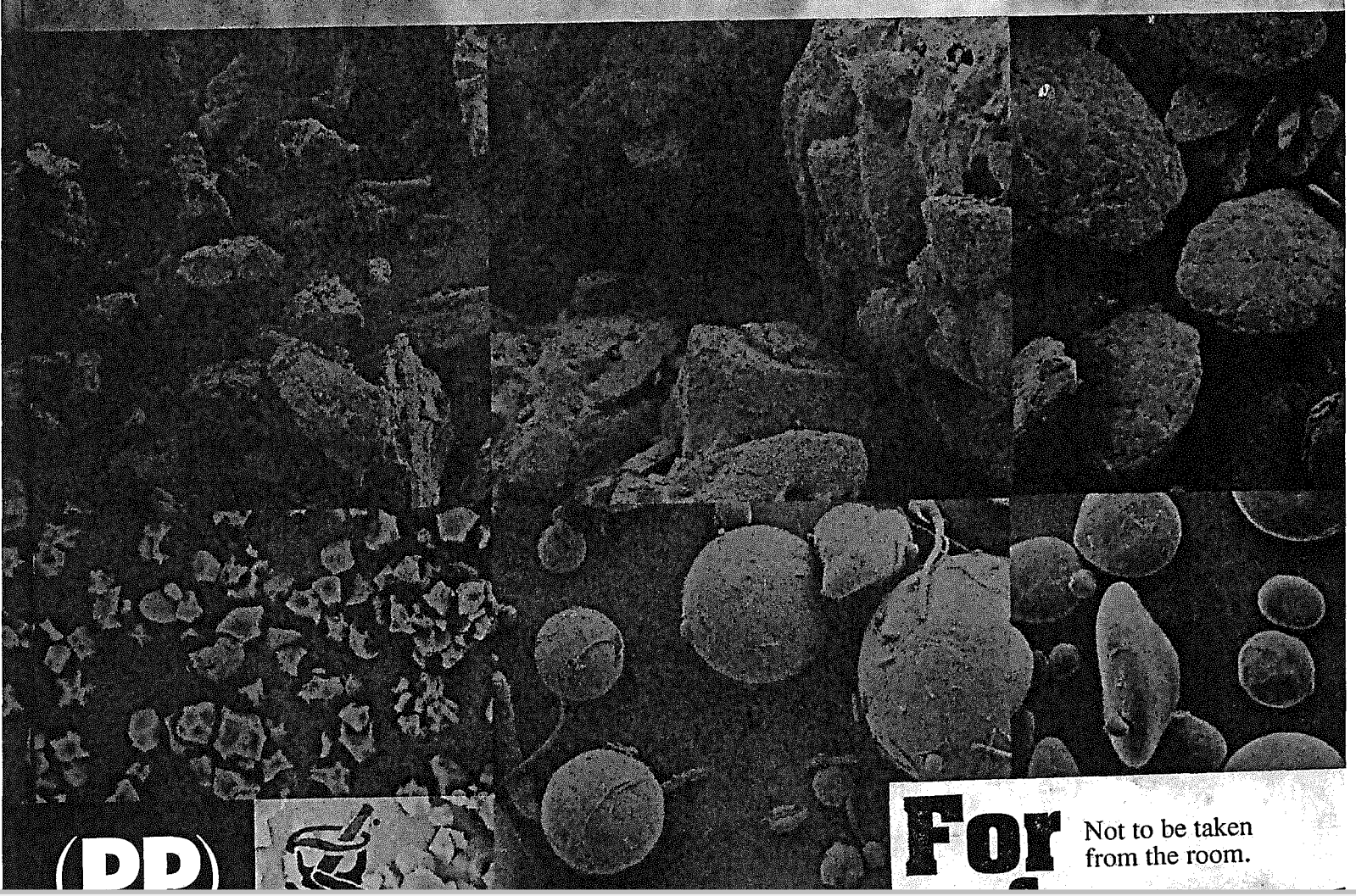


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Handbook of Pharmaceutical Excipients

Sixth edition

Edited by
Raymond C Rowe, Paul J Sheskey and Marian E Quinn



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SIXTH EDITION

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21 Authors

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22 Date of Revision

3 February 2009.

Methylparaben

1 Nonproprietary Names

BP: Methyl Hydroxybenzoate
 JP: Methyl Parahydroxybenzoate
 PhEur: Methyl Parahydroxybenzoate
 USP-NF: Methylparaben

2 Synonyms

Aseptoform M; *CoSept M*; E218; 4-hydroxybenzoic acid methyl ester; metagin; *Methyl Chemosept*; methylis parahydroxybenzoas; methyl *p*-hydroxybenzoate; *Methyl Parasept*; *Nipagin M*; *Solbrol M*; *Tegosept M*; *Uniphen P-23*.

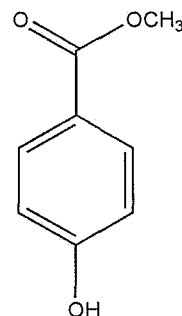
3 Chemical Name and CAS Registry Number

Methyl-4-hydroxybenzoate [99-76-3]

4 Empirical Formula and Molecular Weight

C₉H₈O₃ 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; see Table I for methylparaben uses 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, but aqueous solubility decreases; therefore a mixture of parabens is frequently used to provide effective preservation. Preservative efficacy is also improved by the addition of propylene glycol (2–5%), or by using parabens in combination with other antimicrobial agents such as imidurea; see Section 10.

Owing to the poor solubility of the parabens, paraben salts (particularly the sodium salt) are more frequently used in formulations. However, this raises the pH of poorly buffered formulations.

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

Table I: Uses of methylparaben.

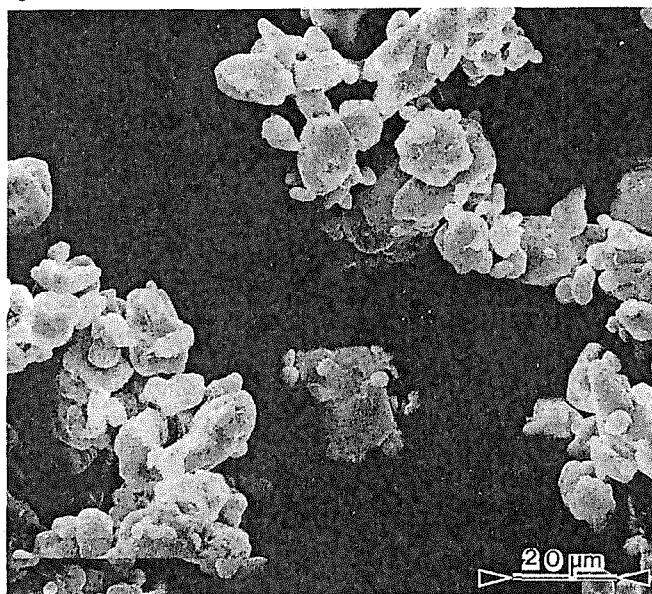
| Use | Concentration (%) |
|--|-------------------|
| IM, IV, SC injections ^(a) | 0.065–0.25 |
| Inhalation solutions | 0.025–0.07 |
| Intradermal injections | 0.10 |
| Nasal solutions | 0.033 |
| Ophthalmic preparations ^(a) | 0.015–0.2 |
| Oral solutions and suspensions | 0.015–0.2 |
| Rectal preparations | 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.

SEM 1: Excipient: methylparaben; supplier: Bate Chemical Co. Ltd; magnification: 600 \times .



9 Pharmacopeial Specifications

See Table II. See also Section 18.

Table II: Pharmacopeial specifications for methylparaben.

| Test | JP XV | PhEur 6.0 | USP32-NF27 |
|------------------------|---------------|--------------|--------------|
| Identification | + | + | + |
| Characters | — | + | — |
| Appearance of solution | + | + | + |
| Acidity | + | + | + |
| Heavy metals | ≤ 20 ppm | — | — |
| Impurities | — | + | — |
| Melting range | — | — | 125–128°C |
| Related substances | + | + | + |
| Sulfated ash | — | $\leq 0.1\%$ | — |
| Residue on ignition | $\leq 0.1\%$ | — | $\leq 0.1\%$ |
| Assay (dried basis) | 98.0–102.0% | 98.0–102.0% | 98.0–102.0% |

10 Typical Properties

Antimicrobial activity see Table III. Methylparaben exhibits antimicrobial activity of pH 4–8. Preservative efficacy decreases with increasing pH owing 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 as synergistic 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 owing 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.

Table III: Minimum inhibitory concentrations (MICs) of methylparaben in aqueous solution.⁽⁴⁾

| Microorganism | MIC ($\mu\text{g/ml}$) |
|--|--------------------------|
| <i>Aerobacter aerogenes</i> ATCC 8308 | 2000 |
| <i>Aspergillus oryzae</i> | 600 |
| <i>Aspergillus niger</i> ATCC 9642 | 1000 |
| <i>Aspergillus niger</i> ATCC 10254 | 1000 |
| <i>Bacillus cereus</i> var. <i>mycooides</i> ATCC 6462 | 2000 |
| <i>Bacillus subtilis</i> ATCC 6633 | 2000 |
| <i>Candida albicans</i> ATCC 10231 | 2000 |
| <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 | 1000 |
| <i>Penicillium chrysogenum</i> ATCC 9480 | 500 |
| <i>Penicillium digitatum</i> ATCC 10030 | 500 |
| <i>Proteus vulgaris</i> ATCC 8427 | 2000 |
| <i>Proteus vulgaris</i> ATCC 13315 | 1000 |
| <i>Pseudomonas aeruginosa</i> ATCC 9027 | 4000 |
| <i>Pseudomonas aeruginosa</i> ATCC 15442 | 4000 |
| <i>Pseudomonas stutzeri</i> | 2000 |
| <i>Rhizopus nigricans</i> ATCC 6227A | 500 |
| <i>Saccharomyces cerevisiae</i> ATCC 9763 | 1000 |
| <i>Salmonella typhosa</i> ATCC 6539 | 1000 |
| <i>Sarcina lutea</i> | 4000 |
| <i>Serratia marcescens</i> ATCC 8100 | 1000 |
| <i>Staphylococcus aureus</i> ATCC 6538P | 2000 |
| <i>Staphylococcus epidermidis</i> ATCC 12228 | 2000 |
| <i>Trichoderma lignorum</i> ATCC 8678 | 250 |
| <i>Trichoderma mentagrophytes</i> | 250 |

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