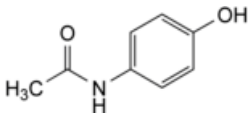
Edition: BP 2025 (Ph. Eur. 11.6 update)

Paracetamol

General Notices

(Ph. Eur. monograph 0049)



$C_8H_9NO_2$ 151.2 *103-90-2*

Action and use

Analgesic; antipyretic.

Preparations

Co-codamol Tablets

Co-codamol Capsules

Co-codamol Effervescent Tablets

Paracetamol Effervescent Tablets

Co-dydramol Tablets

Co-proxamol Tablets

Paracetamol Capsules

Paracetamol Infusion

Paediatric Paracetamol Oral Solution

Paediatric Paracetamol Oral Suspension

Paracetamol Oral Solution

Paracetamol Oral Suspension

Paracetamol Suppositories

Paracetamol Tablets

Paracetamol and Caffeine Tablets

Paracetamol and Caffeine Soluble Tablets

Paracetamol Dispersible Tablets

Paracetamol Soluble Tablets

Paracetamol, Codeine Phosphate and Caffeine Capsules

Paracetamol, Codeine Phosphate and Caffeine Tablets

DEFINITION

N-(4-Hydroxyphenyl)acetamide.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, freely soluble in ethanol (96 per cent), very slightly soluble in methylene chloride.

IDENTIFICATION

First identification: B.

Second identification: A.

A. Melting point (2.2.14).

Determination A Determine the melting point of the substance to be examined.

Result A 168 °C to 172 °C.

Determination B Mix equal parts of the substance to be examined and *paracetamol CRS* and determine the melting point of the mixture.

Result B The absolute difference between the melting point of the mixture and the value obtained in determination A is not greater than 2 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *paracetamol CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *methanol R*, *water R* (15:85 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in 0.75 mL of *methanol R* and dilute to 5.0 mL with *water R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5.0 mg of *paracetamol impurity J CRS* in 25 mL of *methanol R* and dilute to 250.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 200.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5.0 mg of *paracetamol impurity K CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Reference solution (d) Dilute 1.0 mL of reference solution (c) to 10.0 mL with the solvent mixture.

Reference solution (e) Mix 1 mL of reference solution (a) and 1 mL of reference solution (c) and dilute to 10 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped solid core octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: dissolve 1.7 g of *potassium dihydrogen phosphate R* and 1.8 g of *dipotassium hydrogen phosphate R* in *water for chromatography R* and dilute to 1000 mL with the same solvent;

— *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 1.5	95	5
1.5 - 14.4	95 → 90	5 → 10
14.4 - 28.8	90	10
28.8 - 57.6	90 → 66	10 → 34
57.6 - 60	66	34

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Autosampler Set at 5 °C.

Injection 50 µL of the test solution and reference solutions (a), (b), (d) and (e).

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity J; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity K.

Relative retention With reference to paracetamol (retention time = about 4 min): impurity K = about 0.4; impurity J = about 10.1.

System suitability Reference solution (e):

— *resolution*: minimum 5.0 between the peaks due to impurity K and paracetamol.

Calculation of contents:

— for impurity J, use the concentration of impurity J in reference solution (b);

— for impurity K, use the concentration of impurity K in reference solution (d);

— for impurities other than J and K, use the concentration of paracetamol in reference solution (a).

Limits:

— *impurity K*: maximum 50 ppm;

— *impurity J*: maximum 10 ppm;

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.03 per cent, except for impurities J and K.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in a mixture of 10 mL of *water R* and 30 mL of *dilute sulfuric acid R*. Boil under a reflux condenser for 1 h, cool and dilute to 100.0 mL with *water R*. To 20.0 mL of the solution add 40 mL of *water R*, 40 g of ice, 15 mL of *dilute hydrochloric acid R* and 0.1 mL of *ferroin R*. Titrate with *0.1 M cerium sulfate* until a greenish-yellow colour is obtained. Carry out a blank titration.

1 mL of *0.1 M cerium sulfate* is equivalent to 7.56 mg of $C_8H_9NO_2$.

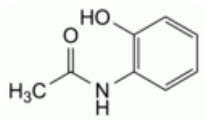
STORAGE

Protected from light.

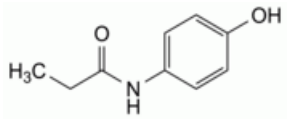
IMPURITIES

Specified impurities J, K.

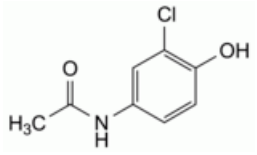
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E, F, G, H, I, L, M, N, O.



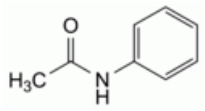
A. *N*-(2-hydroxyphenyl)acetamide,



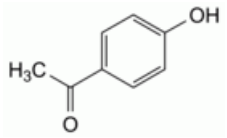
B. *N*-(4-hydroxyphenyl)propanamide,



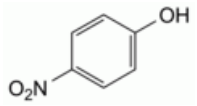
C. *N*-(3-chloro-4-hydroxyphenyl)acetamide,



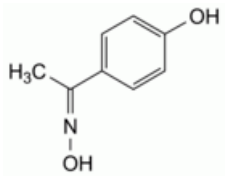
D. *N*-phenylacetamide,



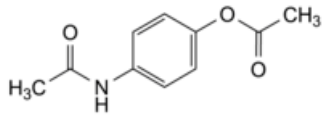
E. 1-(4-hydroxyphenyl)ethan-1-one,



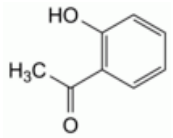
F. 4-nitrophenol,



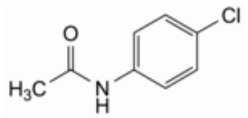
G. [1-(4-hydroxyphenyl)ethylidene]hydroxylamine,



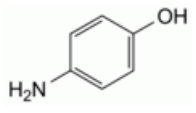
H. 4-acetamidophenyl acetate,



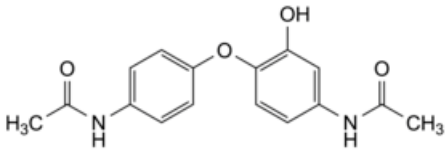
I. 1-(2-hydroxyphenyl)ethan-1-one,



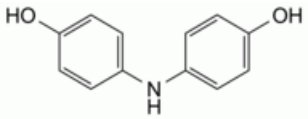
J. *N*-(4-chlorophenyl)acetamide (chloroacetanilide),



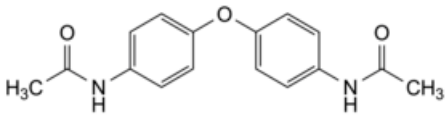
K. 4-aminophenol,



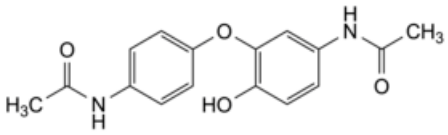
L. *N*-[4-(4-acetamido-2-hydroxyphenoxy)phenyl]acetamide,



M. 4,4′-azanediyldiphenol,



N. *N*,*N*′-[oxydi(4,1-phenylene)]diacetamide,



O. *N*-[4-(5-acetamido-2-hydroxyphenoxy)phenyl]acetamide.

Ph Eur