*System suitability*: reference solution (b):

– *resolution*: minimum 1.5 between the peaks due to impurity A and papaverine.

*Limits*:

– *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 6.2; impurity C = 2.7; impurity D = 0.5;
– *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
– *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);
– *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

**Loss on drying** (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

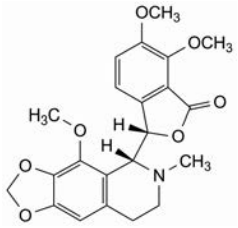
**Sulfated ash** (*2.4.14*): maximum 0.1 per cent, determined on the residue from the test for loss on drying.

ASSAY

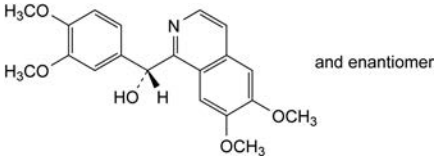
Dissolve 0.300 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *alcohol R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 37.59 mg of $C_{20}H_{22}ClNO_4$.

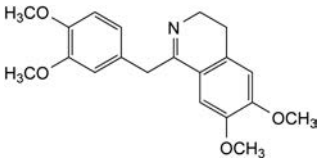
IMPURITIES



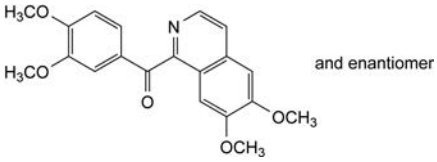
A. (3*S*)-6,7-dimethoxy-3-[(5*R*)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-1,3-dioxolo[4,5-*g*]isoquinolin-5-yl]isobenzofuran-1(3*H*)-one (noscapine),



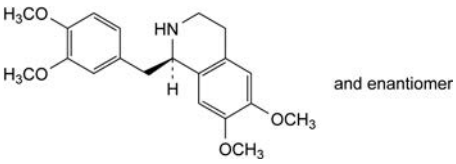

B. (*RS*)-(3,4-dimethoxyphenyl)(6,7-dimethoxyisoquinolin-1-yl)methanol (papaverinol),



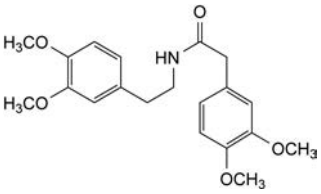
C. 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (dihydropapaverine),




D. (3,4-dimethoxyphenyl)(6,7-dimethoxyisoquinolin-1-yl)methanone (papaveraldine),




E. (1*RS*)-1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (tetrahydropapaverine),

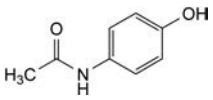


F. 2-(3,4-dimethoxyphenyl)-*N*-[2-(3,4-dimethoxyphenyl)-ethyl]acetamide.

**04/2018:0049**

# PARACETAMOL

## Paracetamolum



$C_8H_9NO_2$ $M_r$ 151.2
[103-90-2]

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 the solvent mixture and dilute to 5.0 mL with the solvent mixture.

*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). Prepare immediately before use.* Dissolve 5.0 mg of *paracetamol impurity K CRS* and 5 mg of *paracetamol CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 100.0 mL with the solvent mixture.

*Reference solution (c).* Dissolve 5.0 mg of *paracetamol impurity J CRS* in the solvent mixture 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.

*Precolumn*:

- *size*: *l* = 0.005 m, Ø = 2.1 mm;
- *stationary phase*: *end-capped solid core octadecylsilyl silica gel for chromatography R* (2.7 µm).

*Column*:

- *size*: *l* = 0.10 m, Ø = 2.1 mm;
- *stationary phase*: *end-capped solid core octadecylsilyl silica gel for chromatography R* (2.7 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 | 95 | 5 |
| 1 - 10 | 95 → 90 | 5 → 10 |
| 10 - 20 | 90 | 10 |
| 20 - 40 | 90 → 66 | 10 → 34 |
| 40 - 50 | 66 | 34 |

*Flow rate*: 0.3 mL/min.

*Detection*: spectrophotometer at 254 nm.

*Injection*: 5 µL.

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

*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 (b):

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

*Calculation of percentage contents*:

- for impurity J, use the concentration of impurity J in reference solution (c);
- for impurity K, use the concentration of impurity K in reference solution (b);
- 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 $C_8H_9NO_2$.

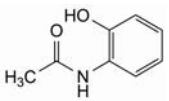
STORAGE

Protected from light.

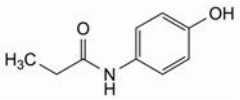
IMPURITIES

*Specified impurities*: *J, K.*

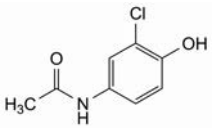
*Other detectable impurities* (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical 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.*



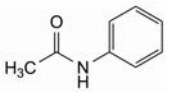
A. *N*-(2-hydroxyphenyl)acetamide,



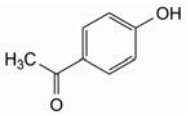
B. *N*-(4-hydroxyphenyl)propanamide,



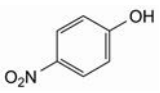
C. *N*-(3-chloro-4-hydroxyphenyl)acetamide,



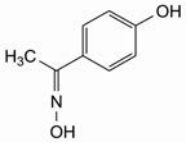
D. *N*-phenylacetamide,



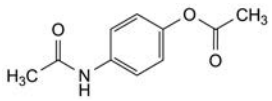
E. 1-(4-hydroxyphenyl)ethan-1-one,



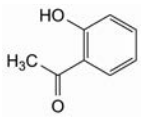
F. 4-nitrophenol,



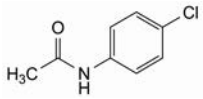
G. [1-(4-hydroxyphenyl)ethylidene]hydroxylamine,



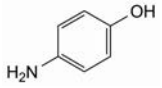
H. 4-acetamidophenyl acetate,



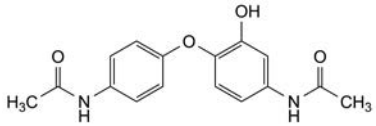
I. 1-(2-hydroxyphenyl)ethan-1-one,



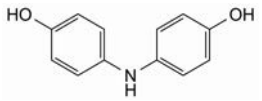
J. *N*-(4-chlorophenyl)acetamide (chloroacetanilide),



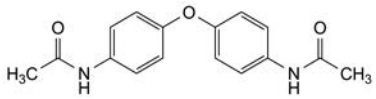
K. 4-aminophenol,



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



M. 4,4′-azanediyldiphenol,



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

**01/2008:1034**

# PARAFFIN, HARD

## Paraffinum solidum

DEFINITION

A purified mixture of solid saturated hydrocarbons generally obtained from petroleum. It may contain a suitable antioxidant.

CHARACTERS

*Appearance*: colourless or white or almost white mass; the melted substance is free from fluorescence in daylight.

*Solubility*: practically insoluble in water, freely soluble in methylene chloride, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

*First identification: A, C.*

*Second identification: B, C.*

A. Infrared absorption spectrophotometry (*2.2.24*).
*Preparation*: place about 2 mg on a sodium chloride plate, heat in an oven at 100 °C for 10 min, spread the melted substance with another sodium chloride plate and remove one of the plates.
*Comparison*: *hard paraffin CRS.*

B. Acidity or alkalinity (see Tests).

C. Melting point (*2.2.16*): 50 °C to 61 °C.

TESTS

**Acidity or alkalinity**. To 15 g add 30 mL of boiling *water R* and shake vigorously for 1 min. Allow to cool and to separate. To 10 mL of the aqueous layer add 0.1 mL of *phenolphthalein solution R*. The solution is colourless. Not more than 1.0 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to red. To a further 10 mL of the aqueous layer add 0.1 mL of *methyl red solution R*. The solution is yellow. Not more than 0.5 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator to red.

**Polycyclic aromatic hydrocarbons**. *Use reagents for ultraviolet absorption spectrophotometry*. Dissolve 0.50 g in 25 mL of *heptane R* and place in a 125 mL separating funnel with unlubricated ground-glass parts (stopper, stopcock). Add 5.0 mL of *dimethyl sulfoxide R*. Shake vigorously for 1 min and allow to stand until 2 clear layers are formed. Transfer the lower layer to a 2nd separating funnel, add 2 mL of *heptane R* and shake the mixture vigorously. Allow to stand until 2 clear layers are formed. Separate the lower layer and measure its absorbance (*2.2.25*) between 265 nm and 420 nm using as the compensation liquid the clear lower layer obtained by vigorously shaking 5.0 mL of *dimethyl sulfoxide R* with 25 mL of *heptane R* for 1 min. Prepare a 7.0 mg/L reference solution of *naphthalene R* in *dimethyl sulfoxide R* and measure the absorbance of this solution at the absorption maximum at 278 nm using *dimethyl sulfoxide R* as the compensation liquid. At wavelengths from 265 nm to 420 nm, the absorbance of the test solution is not greater than one-third that of the reference solution at 278 nm.

**Sulfates** (*2.4.13*): maximum 150 ppm.

Introduce 2.0 g of the melted substance to be examined into a 50 mL ground-glass-stoppered separating funnel. Add 30 mL of boiling *distilled water R*, shake vigorously for 1 min and filter.

STORAGE

Protected from light.

**07/2018:0240**

# PARAFFIN, LIGHT LIQUID

## Paraffinum perliquidum

DEFINITION

Purified mixture of liquid saturated hydrocarbons obtained from petroleum.

CHARACTERS

*Appearance*: colourless, transparent, oily liquid, free from fluorescence in daylight.

*Solubility*: practically insoluble in water, slightly soluble in ethanol (96 per cent), miscible with hydrocarbons.

IDENTIFICATION

*First identification: A, C.*

*Second identification: B, C.*

A. Infrared absorption spectrophotometry (*2.2.24*).
*Comparison*: *Ph. Eur. reference spectrum of liquid paraffin.*