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

Benzoyl Peroxide and Clindamycin Gel

General Notices

Action and use

Used topically in the treatment of acne.

DEFINITION

Benzoyl Peroxide and Clindamycin Gel contains Hydrous Benzoyl Peroxide and Clindamycin Phosphate in a suitable water-miscible basis.

The gel complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of anhydrous benzoyl peroxide, $C_{14}H_{10}O_4$

90.0 to 110.0% of the stated amount.

Content of clindamycin, $C_{18}H_{33}ClN_2O_5S$

92.0 to 107.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.
(1) Shake a quantity of the gel being examined containing the equivalent of 50 mg of anhydrous benzoyl peroxide with 50 mL of *dichloromethane*. Add sufficient *dichloromethane* to produce 100 mL and filter.
(2) Dissolve a quantity of *benzoyl peroxide* containing 25 mg of anhydrous benzoyl peroxide in *dichloromethane* and dilute to 50 mL with the same solvent.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.
(b) Use the mobile phase as described below.
(c) Apply 5 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *glacial acetic acid*, 2 volumes of *dichloromethane* and 50 volumes of *toluene*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.
(1) Shake a quantity of the gel containing the equivalent of 20 mg of clindamycin with 5 mL of *methanol*. Add sufficient *methanol* to produce 10 mL and filter.
(2) 0.24% w/v of *clindamycin phosphate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.
(b) Use the mobile phase as described below.
(c) Apply 5 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry at 100° to 105° for 30 minutes, allow it to cool and spray with a 0.1% w/v solution of *potassium permanganate* and examine in daylight.

MOBILE PHASE

20 volumes of *glacial acetic acid*, 20 volumes of *water* and 60 volumes of *butan-1-ol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

C. In the test for Related substances for benzoyl peroxide, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (5).
D. In the Assay for clindamycin, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

Related substances

For benzoyl peroxide

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the gel containing the equivalent of 50 mg of anhydrous benzoyl peroxide with 50 mL of *acetone*, dilute to 100 mL with *acetone* and centrifuge. Dilute 1 volume of the supernatant liquid to 10 volumes with *acetonitrile*.
(2) Dilute 1 volume of solution (1) to 100 volumes with *acetonitrile*.
(3) 0.003% w/v of *benzoic acid*, 0.0003% w/v of *ethyl benzoate* and 0.0003% w/v of *benzaldehyde* in *acetonitrile*.
(4) Dilute 1 volume of solution (2) to 10 volumes with *acetonitrile*.
(5) 0.005% w/v of *benzoyl peroxide* in a mixture of 1 volume of *acetone* and 9 volumes of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped phenylethyl silica gel for chromatography* (4 µm) (Phenomenex Synergi Polar RP is suitable) fitted with a suitable stainless steel guard column packed with *octadecylsilyl silica gel for chromatography*.
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.3 mL per minute.
(d) Use a column temperature of 35°.
(e) Use a detection wavelength of 235 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.00042% v/v *orthophosphoric acid*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	65	35	isocratic
5-15	65→15	35→85	linear gradient
15-18	15	85	isocratic
18-20	15→65	85→35	linear gradient

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
20-31	65	35	re-equilibration

When the chromatograms are recorded under the prescribed conditions the relative retentions with reference to benzoyl peroxide (retention time about 14 minutes) are: benzoic acid, about 0.3; benzaldehyde, about 0.5 and ethyl benzoate, about 0.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to benzoic acid and benzaldehyde is at least 2.0.

LIMITS

Identify the peaks due to benzoic acid, benzaldehyde and ethyl benzoate using the chromatogram obtained with solution (3) and multiply the areas of these peaks by the corresponding correction factors: benzoic acid, 1.5; benzaldehyde, 1.7; and ethyl benzoate, 1.7.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to benzoic acid is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (5%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the sum of the areas of all the *secondary peaks* excluding benzoic acid is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

For clindamycin

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) 0.002% w/v of *2-phenoxyethanol* *(internal standard)* in 0.1% v/v of *trifluoroacetic acid*.
(2) Shake a quantity of the gel containing the equivalent of 0.1 g of clindamycin with 30 mL of solution (1), dilute to 50 mL with solution (1) and filter.
(3) Disperse with the aid of ultrasound 0.15 g of *clindamycin phosphate BPCRS* and 0.25 g of *benzoyl peroxide* in 10 mL of *water*. Heat at 85° for 16 hours, filter and dilute 1 volume of the filtrate to 25 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Phenomenex Luna C8 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.5 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 210 nm.
(f) Inject 10 µL of each solution.
(g) Allow the chromatography to proceed for twice the retention time of clindamycin.

MOBILE PHASE

0.1 volume of *trifluoroacetic acid*, 17 volumes of *acetonitrile R1* and 83 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to clindamycin (retention time about 30 minutes) are: impurity A, about 0.1; impurity 1, about 0.28; impurity 2, about 0.36; impurity 3, about 0.38; impurity B, about 0.40; impurity 4, about 0.43; benzoic acid, about 0.7; impurity E, about 1.5.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *clindamycin phosphate BPCRS*.

LIMITS

In the chromatogram obtained with solution (2):

Identify the peaks corresponding to impurities A, 1, 2, 3 and 4 using the chromatogram obtained with solution (3). Multiply the heights of these peaks by the corresponding correction factors: impurity A, 0.2; impurity 1, 0.3; impurity 2, 0.4; impurity 3, 0.3; impurity 4, 0.4.

Calculate the ratio (*R*) of the height of the peak corresponding to clindamycin, to the height of the peak corresponding to the internal standard.

the ratio of the height of any peak corresponding to impurity 1 to the height of the peak due to the internal standard is not greater than 0.06*R* (6.0%);

the ratio of the height of any peak corresponding to impurity 2 to the height of the peak due to the internal standard is not greater than 0.02*R* (2.0%);

the ratio of the height of any peak corresponding to impurity 3 to the height of the peak due to the internal standard is not greater than 0.09*R* (9.0%);

the ratio of the height of any other *secondary peak* to the height of the internal standard is not greater than 0.01*R* (1.0%);

the sum of the ratios of the heights of all *secondary peaks* to the height of the internal standard is not greater than 0.15*R* (15.0%);

Disregard any secondary peak where the ratio of the height of the peak is less than 0.01*R* (1.0%).

ASSAY

For benzoyl peroxide

Mix, with the aid of ultrasound, a weighed quantity of the gel containing the equivalent of 10 mg of anhydrous benzoyl peroxide with 5 mL of *dimethylformamide* and 25 mL of *acetone*. Add 5 mL of a 50% w/v solution of *potassium iodide*. Titrate with 0.1M *sodium thiosulfate VS* using *starch solution*, added towards the end of the titration, as indicator. Carry out a blank titration using 5 mL of *dimethylformamide* and 25 mL of *acetone*. The difference between the titrations represents the amount of sodium thiosulfate required. Each mL of 0.1M *sodium thiosulfate VS* is equivalent to 12.11 mg of $C_{14}H_{10}O_4$.

For clindamycin

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) 0.002% w/v of *2-phenoxyethanol (internal standard)* in 0.1% v/v *trifluoroacetic acid*.
(2) Shake a quantity of the gel containing the equivalent of 10 mg of clindamycin with 30 mL of solution (1), dilute to 50 mL with solution (1) and filter.
(3) 0.024% w/v of *clindamycin phosphate BPCRS*.
(4) Disperse with the aid of ultrasound, 0.15 g of *clindamycin phosphate BPCRS* and 0.25 g of *benzoyl peroxide* in 10 mL of *water*. Heat at 85° for 16 hours, filter and dilute 1 volume of the filtrate to 25 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (4) closely resembles the chromatogram supplied with *clindamycin phosphate BPCRS*.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{33}ClN_2O_5S$ in the gel from the chromatograms obtained and from the declared content of $C_{18}H_{34}ClN_2O_8PS$ in *clindamycin phosphate BPCRS*. Each mg of $C_{18}H_{34}ClN_2O_8PS$ is equivalent to 0.8416 mg of

$C_{18}H_{33}ClN_2O_5S$.

STORAGE

Benzoyl Peroxide and Clindamycin Gel should be stored at a temperature of 2° to 8°. It should not be allowed to freeze.

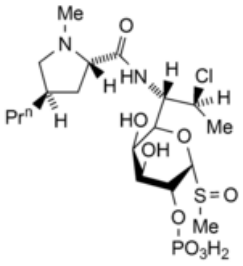
LABELLING

The content of Hydrous Benzoyl Peroxide is stated in terms of the equivalent amount of anhydrous benzoyl peroxide.

The content of Clindamycin Phosphate is stated in terms of the equivalent amount of clindamycin.

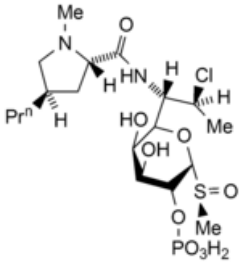
IMPURITIES

The impurities limited by the requirements of this monograph include impurities listed under Hydrous Benzoyl Peroxide, impurities A, B and E listed under Clindamycin Phosphate and the following:

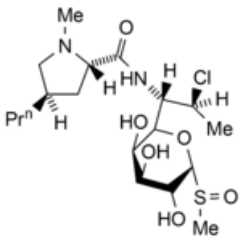


1. [(2*R*,3*R*,4*S*,5*R*,6*R*)-6-[(1*S*,2*S*)-2-Chloro-1-{[(2*S*,4*R*)-1-methyl-4-propylpyrrolidin-2-yl]formamido]propyl]-4,5-dihydroxy-2-[(*R*)-methanesulfinyl]oxan-3-yl dihydrogen phosphate

2. Sulphoxide Steroisomer



3. [(2*R*,3*R*,4*S*,5*R*,6*R*)-6-[(1*S*,2*S*)-2-Chloro-1-{[(2*S*,4*R*)-1-methyl-4-propylpyrrolidin-2-yl]formamido]propyl]-4,5-dihydroxy-2-[(*S*)-methanesulfinyl]oxan-3-yl dihydrogen phosphate



4. (2*S*,4*R*)-*N*-{(1*S*,2*S*)-2-Chloro-1-[(2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-trihydroxy-6-[(ξ)-methanesulfinyl]oxan-2-yl}propyl-1-methyl-4-propylpyrroliin-2-carboxamide