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

Lidocaine and Chlorhexidine Gel

General Notices

Action and use

Local anaesthetic; class I antiarrhythmic and antiseptic.

DEFINITION

Lidocaine and Chlorhexidine Gel is a sterile solution of Lidocaine Hydrochloride Monohydrate containing 0.25% v/v of Chlorhexidine Gluconate Solution 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 lidocaine hydrochloride, $C_{14}H_{22}N_2O,HCl$

95.0 to 105.0% of the stated amount.

Content of chlorhexidine gluconate solution

0.225 to 0.275% v/v.

IDENTIFICATION

To a quantity of the gel containing the equivalent of 80 mg of anhydrous lidocaine hydrochloride add 4 mL of *hydrochloric acid* and heat on a water bath for 10 minutes. Allow to cool, transfer to a separating funnel with the aid of 20 mL of *water*, add 5M *sodium hydroxide* until precipitation is complete and extract with two 20-mL quantities of *chloroform*. Filter the chloroform extracts through *anhydrous sodium sulfate* and evaporate the filtrate to dryness on a water bath using a current of nitrogen. The residue complies with tests A, B and C.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of lidocaine *(RS 202)*.
B. Dissolve 20 mg in 1 mL of *ethanol (96%)*, add 0.5 mL of a 10% w/v solution of *cobalt(II) chloride* and 0.5 mL of 5M *sodium hydroxide* and shake for 2 minutes. A bluish-green precipitate is produced.
C. Dissolve 40 mg in 5 mL of a 1% w/v solution of *cetrimide* and add 1 mL of 5M *sodium hydroxide* and 1 mL of *bromine water*. An orange colour is produced.
D. In the Assay for chlorhexidine gluconate solution, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to chlorhexidine acetate in the chromatogram obtained with solution (1).

TESTS

Aromatic amines

Not more than 8 ppm of 2,6-dimethylaniline and not more than 1.5 ppm of 4-chloroaniline when determined in the following manner. Carry out the method for *gas chromatography*, Appendix III B, using the following solutions.

(1) Shake 0.2 g of the gel with 20 mL of a mixture of 20 volumes of *ether* and 80 volumes of *hexane* and 5 mL of a buffer solution prepared by adjusting the pH of 0.1M *sodium citrate* to 5.0 with 0.2M *sodium hydroxide*, allow to separate and discard the aqueous layer. Shake the organic layer with *anhydrous sodium sulfate* and filter through silica-treated filter paper (Whatman 1PS is suitable), add 100 µL of *heptafluorobutyric anhydride* and shake for 30 seconds. Allow the solution to stand for 2 minutes, add 5 mL of 0.6M *sodium hydrogen carbonate solution*, shake, allow to separate and use the upper layer
(2) Dissolve 80 mg of *2,6-dimethylaniline* in 1 mL of 1M *hydrochloric acid* with the aid of ultrasound, add sufficient *water* to produce 100 mL, dilute 1 volume of this solution to 50 volumes with 0.01M *hydrochloric acid* and further dilute 1 volume to 20 volumes with the same solvent. Shake 2 mL of this solution with 20 mL of a mixture of 20 volumes of *ether* and 80 volumes of *hexane* and 5 mL of 0.6M *sodium hydrogen carbonate solution* and continue in the same manner as for solution (1) beginning at the words 'allow to separate …'.
(3) Dissolve 30 mg of *4-chloroaniline* in 1 mL of 1M *hydrochloric acid* with the aid of ultrasound, add sufficient *water* to produce 200 mL and dilute 1 volume to 50 volumes with the same solvent; further dilute 1 volume to 20 volumes with the same solvent. Shake 2 mL of this solution with 20 mL of a mixture of 20 volumes of *ether* and 80 volumes of *hexane* and 5 mL of 0.6M *sodium hydrogen carbonate solution* and continue in the same manner as for solution (1) beginning at the words 'allow to separate …'.

CHROMATOGRAPHIC CONDITIONS

(a) Use a glass column (1.5 m × 4 mm) packed with *acid-washed, silanised diatomaceous support* (100 to 120 mesh) coated with 15% w/w of cyanopropylmethylphenyl methyl silicone fluid (OV-225 is suitable).
(b) Use *nitrogen* as the carrier gas at a flow rate of 50 mL per minute.
(c) Use isothermal conditions maintained at 190°.
(d) Use an inlet temperature of 200°.
(e) Use an electron capture detector at a temperature of 270°.
(f) Inject 1 µL of each solution.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 2,6-dimethylaniline is not greater than the area of the principal peak in the chromatogram obtained with solution (2);

the area of any peak corresponding to 4-chloroaniline is not greater than the area of the principal peak in the chromatogram obtained with solution (3).

Sterility

Complies with the *test for sterility*, Appendix XVI A.

ASSAY

For anhydrous lidocaine hydrochloride

Disperse a quantity containing the equivalent of 10 mg of anhydrous lidocaine hydrochloride in 20 mL of *water*. Add 5 mL of *acetate buffer pH 2.8*, 120 mL of *chloroform* and 5 mL of *dimethyl yellow and oracet blue 2R solution* and titrate with 0.005M *dioctyl sodium sulfosuccinate VS*, swirling vigorously. Near the end point add the titrant dropwise and, after each addition, swirl vigorously, allow to separate and swirl gently for 5 seconds. The end point is indicated when the colour of the chloroform layer changes from green to pinkish-grey. Repeat the operation without the preparation being examined. The difference between the titrations represents the amount of dioctyl sodium sulfosuccinate required. Each mL of 0.005M *dioctyl sodium sulfosuccinate VS* is equivalent to 1.354 mg of $C_{14}H_{22}N_2O$,HCl. Determine the *weight per mL* of the gel, Appendix V G, and calculate the percentage of $C_{14}H_{22}N_2O$,HCl, weight in volume.

For chlorhexidine gluconate solution

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

(1) Add 5 mL of a 0.080% w/v solution of *diphenylamine* (internal standard) in the mobile phase to 5 mL of a 0.070% w/v solution of *chlorhexidine acetate BPCRS* in the mobile phase and dilute to 100 mL with the mobile phase.
(2) Mix 10 g of the gel with sufficient of the mobile phase to produce 100 mL.

(3) Prepare solution (3) in the same manner as solution (2) but adding 5 mL of the internal standard solution before diluting to 100 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

0.01M *sodium octanesulfonate* in *methanol (73%)* adjusted to pH 3.0 with *glacial acetic acid*

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{30}Cl_2N_{10},2C_6H_{12}O_7$ from the declared content of $C_{22}H_{30}Cl_2N_{10}$ in *chlorhexidine acetate BPCRS*. Each mg of $C_{22}H_{30}Cl_2N_{10}$ is equivalent to 1.776 mg of $C_{22}H_{30}Cl_2N_{10},2C_6H_{12}O_7$. Determine the *weight per mL* of the gel, Appendix V G, and express the result as the percentage volume in volume of Chlorhexidine Gluconate Solution, which contains 20% w/v of $C_{22}H_{30}Cl_2N_{10},2C_6H_{12}O_7$.

LABELLING

The quantity of Lidocaine Hydrochloride is stated in terms of the equivalent amount of anhydrous lidocaine hydrochloride.