SODIUM CROMOGLICATE

Natrii cromoglicae

C₈H₁₄Na₂O₁₁ M, 512.3

01/2008:0562 corrected 6.0

SODIUM CROMOGlicate

DEFINITION
Sodium cromoglicate contains not less than 98.0 per cent and not more than the equivalent of 101.0 per cent of disodium 5,5′-[2-hydroxypropene-1,3-diy]bis(oxy)bis(4-oxo-4H-1-benzopyran-2-carboxylate, calculated with reference to the dried substance.

CHARACTERs
A white or almost white, crystalline powder, hygroscopic, soluble in water, practically insoluble in alcohol.

IDENTIFICATION
First identification: B, D.
Second identification: A, C, D.
A. Dissolve 10.0 mg in phosphate buffer solution pH 7.4 R and dilute to 100.0 ml with the same solvent. Dilute 10.0 ml of this solution to 100.0 ml with the same solvent. Examined between 230 nm and 350 nm (2.2.25), the solution shows two absorption maxima, at 239 nm and 327 nm. The ratio of the absorbance at the maximum at 327 nm to that at the maximum at 239 nm is 0.25 to 0.30.
B. Examine by infrared absorption spectrophotometry (2.2.24), comparing with the spectrum obtained with sodium cromoglicate CRS. Examine the substances prepared as discs.
C. Dissolve about 5 mg in 0.5 ml of methanol R. Add 3 ml of a solution in methanol R containing 5 g/l of aminopyrazolone R and 1 per cent V/V of hydrochloric acid R. Allow to stand for 5 min. The solution shows an intense yellow colour.
D. It gives reaction (a) of sodium (2.3.1).

TESTS
Solution S. Dissolve 0.5 g in carbon dioxide-free water R and dilute to 25 ml with the same solvent.

Appearance of solution. Solution S is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than reference solution BY₅ (2.2.2, Method II).

Acidity or alkalinity. To 10 ml of solution S add 0.1 ml of phenolphthalein solution R. The solution is colourless. Add 0.2 ml of 0.01 M sodium hydroxide. The solution is pink. Add 0.4 ml of 0.01 M hydrochloric acid. The solution is colourless. Add 0.25 ml of methyl red solution R. The solution is red.

Related substances. Examine by thin-layer chromatography (2.2.27), using silica gel GF₃₄₃ as the coating substance.

Test solution. Dissolve 0.2 g of the substance to be examined in a mixture of 1 volume of aceton R, 4 volumes of tetrahydrofuran R and 6 volumes of water R and dilute to 10 ml with the same mixture of solvents.

Reference solution. Dissolve 10 mg of 1,3-bis(2-acetyl-3-hydroxyphenoxo)-2-propanol CRS in chloroform R and dilute to 100 ml with the same solvent.

Apply separately to the plate 5 µl of each solution. Develop over a path of 10 cm using a mixture of 5 volumes of glacial acetic acid R, 50 volumes of ethyl acetate R and 50 volumes of toluene R. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with the test solution, apart from the principal spot (which remains at the starting point), is not more intense than the spot in the chromatogram obtained with the reference solution (0.5 per cent).

Oxalate. Dissolve 0.10 g in 20 ml of water R, add 5.0 ml of iron salicylate solution R and dilute to 50.0 ml with water R. Determine the absorbance (2.2.25) at 480 nm. The absorbance is not more than 0.10.

ASSAY
Dissolve 0.150 g in 20 ml of anhydrous acetic acid R, heating to about 50 °C. Allow to cool. Titrate with 0.1 M perchloric acid, using 0.25 ml of naptholbenzein solution R as indicator until a green colour is obtained.

1 ml of 0.1 M perchloric acid is equivalent to 8.602 mg of C₈H₁₄Na₂O₁₁.

STORAGE
In an airtight container.

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Test solution. Dissolve 0.2 g of the substance to be examined in a mixture of 1 volume of aceton R, 4 volumes of tetrahydrofuran R and 6 volumes of water R and dilute to 10 ml with the same mixture of solvents.

Reference solution. Dissolve 10 mg of 1,3-bis(2-acetyl-3-hydroxyphenoxo)-2-propanol CRS in chloroform R and dilute to 100 ml with the same solvent.

Apply separately to the plate 5 µl of each solution. Develop over a path of 10 cm using a mixture of 5 volumes of glacial acetic acid R, 50 volumes of ethyl acetate R and 50 volumes of toluene R. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with the test solution, apart from the principal spot (which remains at the starting point), is not more intense than the spot in the chromatogram obtained with the reference solution (0.5 per cent).

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1 ml of 0.1 M perchloric acid is equivalent to 8.602 mg of C₈H₁₄Na₂O₁₁.
absorbance is not less than that of a standard prepared in the same manner using 0.35 mg of oxalic acid R instead of the substance to be examined.

**Heavy metals** (2.4.8). 1.0 g complies with limit test C for heavy metals (20 ppm). Prepare the standard using 2 ml of lead standard solution (10 ppm Pb) R.

**Loss on drying** (2.2.32). Not more than 10.0 per cent, determined on 1.000 g by drying over diphenylphosphorus pentoxide R at 105 °C and at a pressure of 300 Pa to 600 Pa.

**ASSAY**
Dissolve 0.200 g with heating in a mixture of 5 ml of 2-propanol R and 25 ml of ethylene glycol R. Cool and add 30 ml of dioxan R. Titrate with 0.1 M perchloric acid, determining the end-point potentiometrically (2.2.20).

1 ml of 0.1 M perchloric acid is equivalent to 25.62 mg of C_{23}H_{14}Na_{2}O_{11}.

**STORAGE**
Store in an airtight container, protected from light.

**01/2008:0774**
**corrected 6.0**

**SODIUM CYCLAMATE**

**Natrii cyclamas**

\[
\text{C}_{23}\text{H}_{14}\text{Na}_{2}\text{O}_{11} \quad M, 201.2
\]

**DEFINITION**
Sodium N-cyclohexylsulphamate.

**Content**: 98.5 per cent to 101.0 per cent (dried substance).

**CHARACTERS**

**Appearance**: white or almost white, crystalline powder or colourless crystals.

**Solubility**: freely soluble in water, slightly soluble in ethanol (96 per cent).

**IDENTIFICATION**

**First identification**: A, E.

**Second identification**: B, C, D, E.

A. Infrared absorption spectrophotometry (2.2.24).

**Comparison**: sodium cyclamate CRS.

B. Examine the chromatograms obtained in the test for impurity A.

**Results**: the principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. To 1 ml of solution S (see Tests), add 1 ml of water R and 2 ml of silver nitrate solution R1, then shake. A white, crystalline precipitate is formed.

D. To 1 ml of solution S add 5 ml of water R, 2 ml of dilute hydrochloric acid R and 4 ml of barium chloride solution R1 and mix. The solution is clear. Add 2 ml of sodium nitrite solution R. A voluminous white precipitate is formed and gas is given off.

E. A mixture of 1 ml of solution S and 1 ml of water R gives reaction (a) of sodium (2.3.1).

**TESTS**

**Solution S**. Dissolve 5 g in carbon dioxide-free water R prepared from distilled water R and dilute to 50 ml with the same solvent.

**Appearance of solution**. Solution S is clear (2.2.1) and colourless (2.2.2, Method II).

**pH** (2.2.3): 5.5 to 7.5 for solution S.

**Absorbance** (2.2.25): maximum 0.10, determined at 270 nm on solution S.

**Impurity A**. Thin-layer chromatography (2.2.27).

**Test solution (a)**. Solution S.

**Test solution (b)**. Dilute 1 ml of test solution (a) to 10 ml with water R.

**Reference solution (a)**. Dissolve 0.10 g of sodium cyclamate CRS in water R and dilute to 10 ml with the same solvent.

**Reference solution (b)**. Dissolve 10 mg of sulphamic acid R (impurity A) in water R and dilute to 100 ml with the same solvent.

**Plate**: TLC silica gel G plate R.


**Application**: 2 µl.

**Development**: over a path of 12 cm.

**Drying**: in a current of warm air, then heat at 105 °C for 5 min.

**Detection**: spray the hot plate with strong sodium hypochlorite solution R diluted to a concentration of 5 g/l of active chlorine. Place in a current of cold air until an area of coating below the points of application gives at most a faint blue colour with a drop of potassium iodide and starch solution R; avoid prolonged exposure to cold air. Spray with potassium iodide and starch solution R and examine the chromatograms within 5 min.

**Limit**: test solution (a):

- impurity A: any spot due to impurity A is not more intense than the corresponding spot in the chromatogram obtained with reference solution (b) (0.1 per cent).

**Impurities B, C and D**. Gas chromatography (2.2.28).

**Internal standard solution**. Dissolve 2 µl of tetradecane R in methylene chloride R and dilute to 100 ml with the same solvent.

**Test solution**. Dissolve 2.00 g of the substance to be examined in 20 ml of water R, add 0.5 ml of strong sodium hydroxide solution R and shake with 30 ml of toluene R. Shake 20 ml of the upper layer with 4 ml of a mixture of equal volumes of dilute acetic acid R and water R. Separate the lower layer, add 0.5 ml of strong sodium hydroxide solution R and 0.5 ml of the internal standard solution and shake. Use the lower layer immediately after separation.

**Reference solution**. Dissolve 10.0 mg (about 12 µl) of cyclohexylamine R (impurity C), 1.0 mg (about 1.1 µl) of dicyclohexylamine R (impurity D) and 1.0 mg (about 1 µl) of aniline R (impurity B) in water R, then dilute to 1000 ml with the same solvent. Dilute 10.0 ml of this solution to 100.0 ml with water R (solution A). To 20.0 ml of solution A, add 0.5 ml of strong sodium hydroxide solution R and extract with 30 ml of toluene R. Shake 20 ml of the upper layer with 4 ml of a mixture of equal volumes of dilute acetic acid R and water R. Separate the lower layer, add 0.5 ml of strong sodium hydroxide solution R and 0.5 ml of the internal standard solution and shake. Use the lower layer immediately after separation.