Readily carbonisable substances. To 0.20 g of the powdered substance to be examined add 10 ml of *sulphuric acid R* and heat in a water-bath at 90 ± 1 °C for 60 min. Cool rapidly. The solution is not more intensely coloured than reference solution Y_2 or GY_2 (*2.2.2, Method II*).

Chlorides (*2.4.4*): maximum 50 ppm.

Dilute 10 ml of solution S to 15 ml with *water R*.

Oxalates: maximum 300 ppm.

Dissolve 0.50 g in 4 ml of *water R*, add 3 ml of *hydrochloric acid R* and 1 g of *zinc R* in granules and heat on a water-bath for 1 min. Allow to stand for 2 min, decant the liquid into a test-tube containing 0.25 ml of a 10 g/l solution of *phenylhydrazine hydrochloride R* and heat to boiling. Cool rapidly, transfer to a graduated cylinder and add an equal volume of *hydrochloric acid R* and 0.25 ml of *potassium ferricyanide solution R*. Shake and allow to stand for 30 min. Any pink colour in the solution is not more intense than that in a standard prepared at the same time in the same manner using 4 ml of a 50 mg/l solution of *oxalic acid R*.

Sulphates (*2.4.13*): maximum 150 ppm.

To 10 ml of solution S add 2 ml of *hydrochloric acid R1* and dilute to 15 ml with *distilled water R*.

Heavy metals (*2.4.8*): maximum 10 ppm.

12 ml of solution S complies with test A. Prepare the reference solution using *lead standard solution (1 ppm Pb) R*.

Water (*2.5.12*): 11.0 per cent to 13.0 per cent, determined on 0.300 g. After adding the substance to be examined, stir for 15 min before titrating.

Pyrogens (*2.6.8*). If intended for use in the manufacture of large-volume parenteral dosage forms, the competent authority may require that it comply with the test for pyrogens. Inject per kilogram of the rabbit's mass 10 ml of a freshly prepared solution in *water for injections R* containing per millilitre 10.0 mg of the substance to be examined and 7.5 mg of pyrogen-free *calcium chloride R*.

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 *naphtholbenzein 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 $C_6H_5Na_3O_7$.

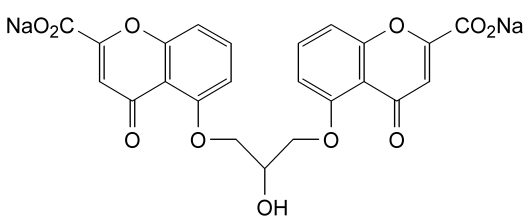
STORAGE

In an airtight container.

01/2008:0562
corrected 6.0

SODIUM CROMOGLICATE

Natrii cromoglicas



$C_{23}H_{14}Na_2O_{11}$ M_r 512.3
[15826-37-6]

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-hydroxypropane-1,3-diyl)bis(oxy)]bis(4-oxo-4*H*-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 BY_5 (*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* GF_{254} *R* as the coating substance.

Test solution. Dissolve 0.2 g of the substance to be examined in a mixture of 1 volume of *acetone 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-hydroxyphenoxy)-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 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 *diphosphorus 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 $C_{23}H_{14}Na_2O_{11}$.

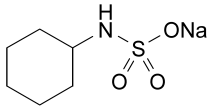
STORAGE

Store in an airtight container, protected from light.

01/2008:0774
corrected 6.0

SODIUM CYCLAMATE

Natrii cyclamas



$C_6H_{12}NNaO_3S$ M_r 201.2
[139-05-9]

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.*

Mobile phase: *concentrated ammonia R, water R, ethyl acetate R, propanol R* (10:10:20:70 *V/V/V/V*).

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.