UNIVERSITÀ DEGLI STUDI DI TORINO

ESAME DI STATO PER L'ABILITAZIONE ALL'ESERCIZIO DELLA PROFESSIONE DI FARMACISTA

PRIMA SESSIONE 2017

PROVA SCRITTA

Tema n. 1
Le preparazioni oftalmiche liquide: tipologia, caratteristiche e requisiti.

Tema n. 2
Le ispezioni in farmacia, normativa e ultima check list.

Tema n. 3
Gli antiepilettici.

PROVA PRATICA

Prova n.1
Dosamento del farmaco.
Vedi allegato di seguito.

Prova n.2
Riconoscimento del farmaco.
Vedi allegato di seguito.

Prova n.3
Spedizione della ricetta.
Vedi allegato di seguito.

UNIVERSITA' DEGLI STUDI DI TORINO
ESAME DI STATO PER L'ABILITAZIONE ALL'ESERCIZIO DELLA PROFESSIONE DI FARMACISTA

PRIMA SESSIONE 2017

PROVA PRATICA-DOSAMENTO DEL FARMACO

Cognome e nome.....

Cinque compresse dal peso complessivo di 2,500 g contenenti diclofenac sale sodico (PM=318.1) ed eccipienti inerti sono state polverizzate. 1,500 g di polvere è stata sciolta in un matraccio da 50,00 mL con acido acetico anidro e portata a volume per ottenere la soluzione A.

25,00 mL della soluzione A sono stati esattamente prelevati e titolati secondo Ph. Eur. 9.2. La titolazione ha richiesto 11.802 mL di acido perclorico ($HClO_4$) 0.1000 M.

Si calcolino:

a) i grammi di diclofenac sale sodico contenuti in una compressa
b) la % di principio attivo contenuti in una compressa
c) la concentrazione molare del diclofenac sale sodico nella soluzione A

Risposte ai quesiti:

a) _____

b) _____

c) _____

N.B. Insieme alla prova al candidato viene fornita copia della monografia ufficiale di Ph. Eur. 9.2 del diclofenac sale sodico

Identification of impurities: use the chromatogram supplied with *diclofenac for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and F.

Relative retention with reference to diclofenac (retention time = about 25 min): impurity A = about 0.4; impurity F = about 0.8.

System suitability: reference solution (b):

- *resolution*: minimum 4.0 between the peaks due to impurity F and diclofenac.

Calculation of percentage contents:

- *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.7; impurity F = 0.3;
- for each impurity, use the concentration of diclofenac in reference solution (a).

Limits:

- *impurities A, F*: for each impurity, maximum 0.15 per cent;
- *unspecified impurities*: for each impurity, maximum 0.10 per cent;
- *total*: maximum 0.4 per cent;
- *reporting threshold*: 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 for 3 h.

ASSAY

Dissolve 0.250 g in 60 mL of *anhydrous acetic acid 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 33.42 mg of $C_{14}H_{10}Cl_2KNO_2$.

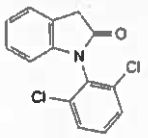
STORAGE

In an airtight container, protected from light.

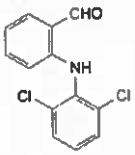
IMPURITIES

Specified impurities: A, F.

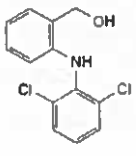
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



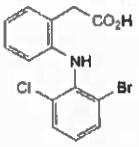
A. 1-(2,6-dichlorophenyl)-1,3-dihydro-2*H*-indol-2-one,



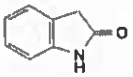
B. 2-[(2,6-dichlorophenyl)amino]benzaldehyde,



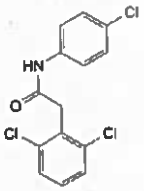
C. [2-[(2,6-dichlorophenyl)amino]phenyl]methanol,



D. [2-[(2-bromo-6-chlorophenyl)amino]phenyl]acetic acid,



E. 1,3-dihydro-2*H*-indol-2-one,



F. *N*-(4-chlorophenyl)-2-(2,6-dichlorophenyl)acetamide.

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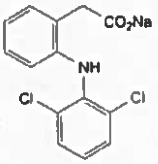
DICLOFENAC SODIUM

Diclofenacum natricum



$C_{14}H_{10}Cl_2NNaO_2$ M_r 318.1

[15307-79-6]

DEFINITION

Sodium [2-[(2,6-dichlorophenyl)amino]phenyl]acetate.

Content: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or slightly yellowish, slightly hygroscopic, crystalline powder.

Solubility: sparingly soluble in water, freely soluble in methanol, soluble in ethanol (96 per cent), slightly soluble in acetone.

mp: about 280 °C, with decomposition.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: diclofenac sodium CRS.

B. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 25 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (a). Dissolve 25 mg of *diclofenac sodium CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (b). Dissolve 10 mg of *indometacin R* in reference solution (a) and dilute to 2 mL with reference solution (a).

Plate: *TLC silica gel GF_{254} plate R.*

Mobile phase: *concentrated ammonia R, methanol R, ethyl acetate R* (10:10:80 *V/V/V*).

Application: 5 µL.

Development: over 1/2 of the plate.

Drying: in air.

Detection: examine in ultraviolet light at 254 nm.

System suitability: reference solution (b):

- the chromatogram shows 2 clearly separated spots.

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

C. Dissolve about 10 mg in 10 mL of *ethanol (96 per cent) R*. To 1 mL of this solution add 0.2 mL of a mixture, prepared immediately before use, of equal volumes of a 6 g/L solution of *potassium ferricyanide R* and a 9 g/L solution of *ferric chloride R*. Allow to stand protected from light for 5 min. Add 3 mL of a 10 g/L solution of *hydrochloric acid R*. Allow to stand, protected from light, for 15 min. A blue colour develops and a precipitate is formed.

D. Dissolve 60 mg in 0.5 mL of *methanol R* and add 0.5 mL of *water R*. The solution gives reaction (b) of sodium (*2.3.1*).

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and its absorbance (*2.2.25*) at 440 nm is not greater than 0.05.

Dissolve 1.25 g in *methanol R* and dilute to 25.0 mL with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a). Dilute 2.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b). Dissolve the contents of a vial of *diclofenac for system suitability CRS* (containing impurities A and F) in 1.0 mL of the mobile phase.

Column:

- size: l = [illegible] = 4.6 mm;
- *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: mix 34 volumes of a solution containing 0.5 g/L of *phosphoric acid R* and 0.8 g/L of *sodium dihydrogen phosphate R*, previously adjusted to pH 2.5 with *phosphoric acid R*, and 66 volumes of *methanol R*.

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 254 nm.

Injection: 20 µL.

Run time: 1.6 times the retention time of diclofenac.

Identification of impurities: use the chromatogram supplied with *diclofenac for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and F.

Relative retention with reference to diclofenac (retention time = about 25 min): impurity A = about 0.4; impurity F = about 0.8.

System suitability: reference solution (b):

- *resolution*: minimum 4.0 between the peaks due to impurity F and diclofenac.

Calculation of percentage contents:

- *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.7; impurity F = 0.3;
- for each impurity, use the concentration of diclofenac in reference solution (a).

Limits:

- *impurity A*: maximum 0.2 per cent;
- *impurity F*: maximum 0.15 per cent;
- *unspecified impurities*: for each impurity, maximum 0.10 per cent;
- *total*: maximum 0.4 per cent;
- *reporting threshold*: 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 for 3 h.

ASSAY

Dissolve 0.250 g in 60 mL of *anhydrous acetic acid 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 31.81 mg of $C_{14}H_{10}Cl_2NNaO_2$.

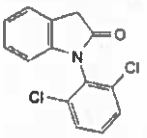
STORAGE

In an airtight container, protected from light.

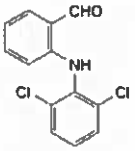
IMPURITIES

Specified impurities: A, F.

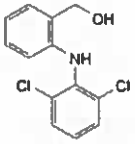
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



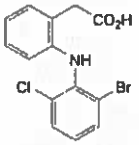
A. 1-(2,6-dichlorophenyl)-1,3-dihydro-2*H*-indol-2-one,



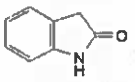
B. 2-[(2,6-dichlorophenyl)amino]benzaldehyde,



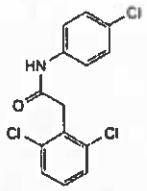
C. [2-[(2,6-dichlorophenyl)amino]phenyl]methanol,



D. [2-[(2-bromo-6-chlorophenyl)amino]phenyl]acetic acid,



E. 1,3-dihydro-2*H*-indol-2-one.

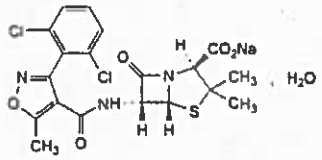


F. *N*-(4-chlorophenyl)-2-(2,6-dichlorophenyl)acetamide.

01/2008:0663
corrected 6.0

DICLOXACILLIN SODIUM

Dicloxacillinum natricum



$C_{19}H_{16}Cl_2N_3NaO_5S,H_2O$ M_r 510.3
[13412-64-1]

DEFINITION

Sodium (2*S*,5*R*,6*R*)-6-[[[3-(2,6-dichlorophenyl)-5-methyl-1,2-oxazol-4-yl]carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate monohydrate.

Semi-synthetic product derived from a fermentation product.

Content: 95.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, hygroscopic, crystalline powder.

Solubility: freely soluble in water, soluble in ethanol (96 per cent) and in methanol.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *dicloxacillin sodium CRS*.

B. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 25 mg of the substance to be examined in 5 mL of *water R*.

Reference solution (a). Dissolve 25 mg of *dicloxacillin sodium CRS* in 5 mL of *water R*.

Reference solution (b). Dissolve 25 mg of *cloxacillin sodium CRS*, 25 mg of *dicloxacillin sodium CRS* and 25 mg of *flucloxacillin sodium CRS* in 5 mL of *water R*.

Plate: *TLC silanised silica gel plate R*.

Mobile phase: mix 30 volumes of *acetone R* and 70 volumes of a 154 g/L solution of *ammonium acetate R* adjusted to pH 5.0 with *glacial acetic acid R*.

Application: 1 µL.

Development: over a path of 15 cm.

Drying: in air.

Detection: expose to iodine vapour until the spots appear and examine in daylight.

System suitability: reference solution (b):

- the chromatogram shows 3 clearly separated spots.

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

C. Place about 2 mg in a test-tube about 150 mm long and about 15 mm in diameter. Moisten with 0.05 mL of *water R* and add 2 mL of *sulfuric acid-formaldehyde reagent R*. Mix the contents of the tube by swirling; the solution is slightly greenish-yellow. Place the test-tube in a water-bath for 1 min; a yellow colour develops.

D. It gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S. Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and its absorbance (*2.2.25*) at 430 nm is not greater than 0.04.

pH (*2.2.3*): 5.0 to 7.0 for solution S.

Specific optical rotation (*2.2.7*): + 128 to + 143 (anhydrous substance).

Dissolve 0.250 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution (a). Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Test solution (b). Dilute 5.0 mL of test solution (a) to 50.0 mL with the mobile phase.

Reference solution (a). Dissolve 50.0 mg of *dicloxacillin sodium CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (b). Dilute 5.0 mL of test solution (b) to 50.0 mL with the mobile phase.

Reference solution (c). Dissolve 5 mg of *flucloxacillin sodium CRS* and 5 mg of *dicloxacillin sodium CRS* in the mobile phase, then dilute to 50.0 mL with the mobile phase.

Column:

- *size*: *l* = 0.25 m, Ø = 4 mm;
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: mix 25 volumes of *acetonitrile R* and 75 volumes of a 2.7 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 5.0 with *dilute sodium hydroxide solution R*.

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 225 nm.

Injection: 20 µL of test solution (a) and reference solutions (b) and (c).

Run time: 5 times the retention time of dicloxacillin.

Retention time: dicloxacillin = about 10 min.

System suitability: reference solution (c):

- *resolution*: minimum 2.5 between the peaks due to flucloxacillin (1st peak) and dicloxacillin (2nd peak).

Limits:

- *any impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent);
- *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (5 per cent);
- *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

***N*,*N*-Dimethylaniline** (*2.4.26, Method B*): maximum 20 ppm.

2-Ethylhexanoic acid (*2.4.28*): maximum 0.8 per cent *m/m*.

Università di Torino
Esame di Stato per l' abilitazione alla Professione di Farmacista

Prima Sessione 2017

PROVA PRATICA-RICONOSCIMENTO DEL FARMACO

Cognome e nome……

La prova consiste nel ***riconoscimento di due farmaci***

Per ogni farmaco viene fornito il profilo sperimentale (sequenza delle analisi effettuate) ed una indicazione di possibili farmaci candidati corredati dalle rispettive monografie provenienti dalla Farmacopea Europea (Ph. Eur. 9.2).

Al candidato viene richiesto di:

1. individuare il farmaco che meglio corrisponde al profilo fornito;
2. motivare brevemente la propria scelta;
3. proporre ulteriori prove sperimentali a conferma della scelta effettuata.

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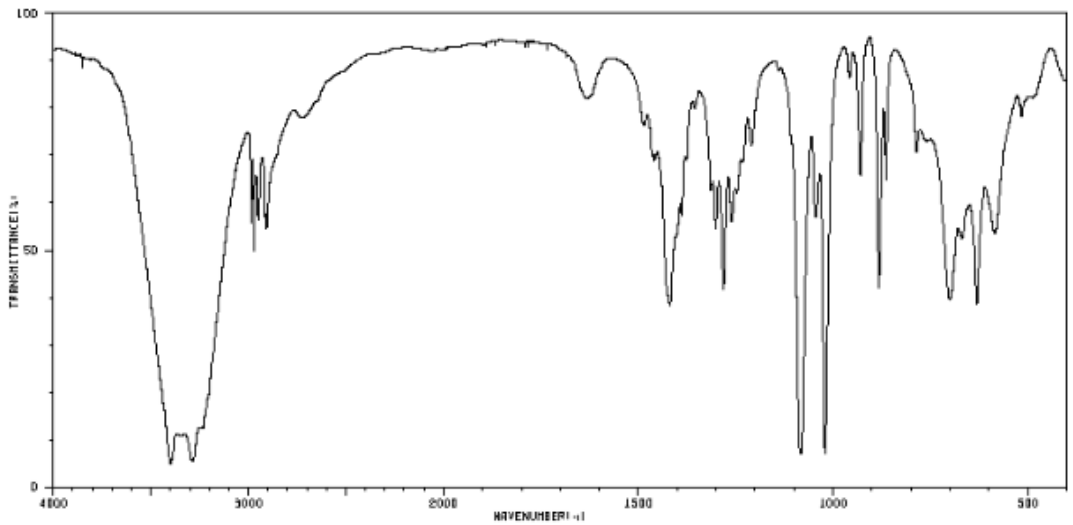
Primo riconoscimento

Il Farmaco in esame si mostra come una polvere bianca cristallina. All'analisi elementare risulta contenere i seguenti elementi: C, H, O. In termini di solubilità il composto si scioglie in acqua (intervallo: da 50 μl a 500 μl) ma debolmente in Etanolo (intervallo: >500 mL). La solubilità non sembra migliorare quando si utilizzano soluzioni acquosa acide o basiche. Il farmaco risulta in grado di ruotare positivamente la luce polarizzata.

Come prescritto dalla farmacopea si è registrato lo spettro IR del farmaco incognito e sotto è riportato lo spettro ottenuto.



Il Farmaco non mostra sensibilità a freddo a soluzioni di Ag(I), Cu(II) e Fe(III) e mostra punto di fusione molto elevato, tanto che questo test non viene utilizzato in FU per il riconoscimento. Se il saggio di esposizione a soluzioni di Ag(I) e Cu(II) viene condotto riscaldando, non si osserva positività.

Nel gruppo di Farmaci a vostra disposizione avete selezionato quali candidati il ***Mannitolo*** e il ***Glucosio*** quali possibili candidati.

1) Indicare quale fra i due Farmaci risponde meglio al profilo sperimentale fornito, giustificando brevemente i criteri che hanno governato la selezione.
2) Quale passo successivo, proporre alcune ulteriori analisi/test che potrebbero meglio validare la scelta effettuata nel primo punto.

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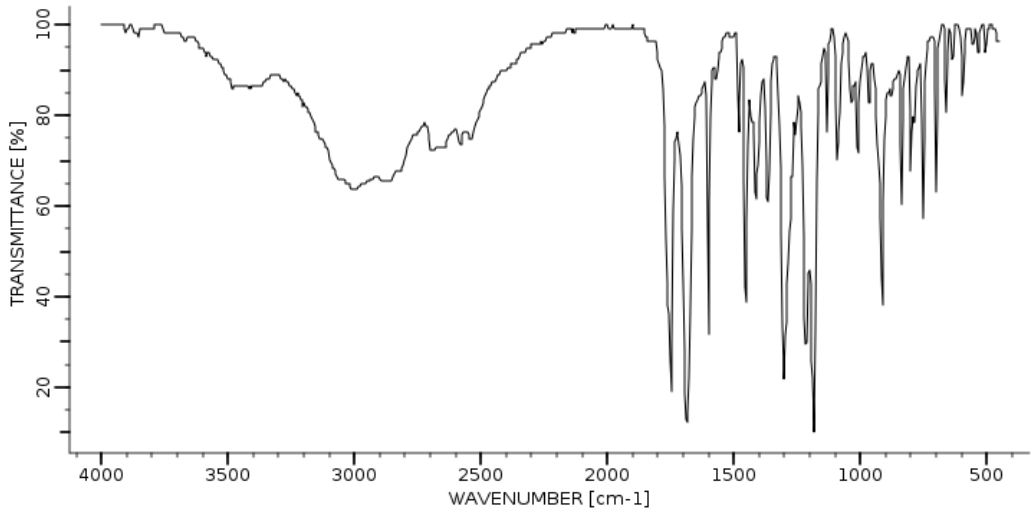
Secondo riconoscimento

Il Farmaco in esame si mostra come una polvere bianca cristallina. All'analisi elementare risulta contenere i seguenti elementi: C, H, O. In termini di solubilità il composto si scioglie debolmente in acqua (intervallo da 5 mL a 50 mL) ma molto meglio in Etanolo (intervallo: da 50 μl a 500 μl). La solubilità migliora quando lo si scioglie in una soluzione di NaOH 2M.

Come prescritto dalla farmacopea si è registrato lo spettro IR del farmaco incognito e sotto è riportato lo spettro ottenuto.



Il Farmaco non mostra sensibilità a soluzioni di Ag(I), Cu(II) e Fe(III) e mostra un punto di fusione inferiore ai 170°C. Se trattato con una soluzione acquosa di NaOH a caldo per alcuni minuti, si trasforma in un derivato a punto di fusione superiore. Quest'ultimo derivato, sebbene risulti ancora insensibile a soluzioni di Ag(I), Cu(II), mostra capacità di viraggio di colore per trattamento con soluzioni di Fe(III).

Nel gruppo di Farmaci a vostra disposizione avete selezionato quali candidati l'***Acido salicilico*** e l' ***Acido Acetil Salicilico*** quali possibili candidati.

1) Indicare quale fra i due Farmaci risponde meglio al profilo sperimentale fornito, giustificando brevemente i criteri che hanno governato la selezione.
2) Quale passo successivo, proporre alcune ulteriori analisi/test che potrebbero meglio validare la scelta effettuata nel primo punto.

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Descriptive term	Approximate volume of solvent (in millilitres for 50 mg of solute)			
Very soluble	less than	50 µl	///	///
Freely soluble	from	50 µl	to	500 µl
Soluble	from	500 µl	to	1.5 ml
Sparingly soluble	from	1.5 ml	to	5 ml
Slightly soluble	from	5 ml	to	50 ml
Very slightly soluble	from	50 ml	to	500 ml
Practically insoluble	more than			500 ml

07/2017:1543

MANGANESE SULFATE MONOHYDRATE

Mangani sulfas monohydricus

$MnSO_4,H_2O$ M_r 169.0
[10034-96-5]

DEFINITION

Content: 99.0 per cent to 101.0 per cent (ignited substance).

CHARACTERS

Appearance: pale pink crystalline powder, slightly hygroscopic.

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

IDENTIFICATION

A. Solution S (see Tests) gives reaction (a) of sulfates (*2.3.1*).

B. Dissolve 50 mg in 5 mL of *water R*. Add 0.5 mL of *sodium sulfide solution R*. A pale pink precipitate is formed which dissolves on the addition of 1 mL of *anhydrous acetic acid R*.

C. Loss on ignition (see Tests).

TESTS

Solution S. Dissolve 10.0 g in *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution. Solution S is not more opalescent than reference suspension II (*2.2.1*).

Chlorides (*2.4.4*): maximum 100 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Iron (*2.4.9*): maximum 10 ppm, determined on solution S.

Zinc: maximum 50 ppm.

To 10 mL of solution S add 1 mL of *sulfuric acid R* and 0.1 mL of *potassium ferrocyanide solution R*. After 30 s, any opalescence in the solution is not more intense than that in a mixture of 5 mL of *zinc standard solution (10 ppm Zn) R*, 5 mL of *water R*, 1 mL of *sulfuric acid R* and 0.1 mL of *potassium ferrocyanide solution R*.

Loss on ignition: 10.0 per cent to 12.0 per cent, determined on 1.00 g at 500 ± 50 °C.

ASSAY

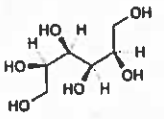
Dissolve 0.150 g in 50 mL of *water R*. Add 10 mg of *ascorbic acid R*, 20 mL of *ammonium chloride buffer solution pH 10.0 R* and 0.2 mL of a 2 g/L solution of *mordant black 11 R* in *triethanolamine R*. Titrate with *0.1 M sodium edetate* until the colour changes from violet to pure blue.

1 mL of *0.1 M sodium edetate* is equivalent to 15.10 mg of $MnSO_4$.

01/2017:0559
corrected 9.2

MANNITOL(1)

Mannitolum



$C_6H_{14}O_6$ M_r 182.2
[69-65-8]

DEFINITION

D-Mannitol.

Content: 97.0 per cent to 102.0 per cent (dried substance).

◆CHARACTERS

Appearance: white or almost white crystals or powder.

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

It shows polymorphism (*5.9*).◆

IDENTIFICATION

First identification: C.

◊*Second identification*: A, B, D.

A. Specific optical rotation (*2.2.7*): + 23 to + 25 (dried substance).

Dissolve 2.00 g of the substance to be examined and 2.6 g of *disodium tetraborate R* in about 20 mL of *water R* at 30 °C; shake continuously for 15-30 min without further heating. Dilute the resulting clear solution to 25.0 mL with *water R*.

B. Melting point (see Tests).◊

C. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *mannitol CRS*.

If the spectra obtained in the solid state show differences, dissolve separately in 2 glass vials 25 mg of the substance to be examined and 25 mg of the reference substance in 0.25 mL of *distilled water R* without heating. The solutions obtained are clear. Evaporate to dryness by heating in a microwave oven with a power range of 600-700 W for 20 min or by heating in an oven at 100 °C for 1 h then gradually applying vacuum until a dry residue is obtained. Non-sticky, white or slightly yellowish powders are obtained. Record new spectra using the residues.

◊D. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 25 mg of the substance to be examined in *water R* and dilute to 10 mL with the same solvent.

Reference solution (a). Dissolve 25 mg of *mannitol CRS* in *water R* and dilute to 10 mL with the same solvent.

Reference solution (b). Dissolve 25 mg of *mannitol R* and 25 mg of *sorbitol R* in *water R* and dilute to 10 mL with the same solvent.

Plate: *TLC silica gel plate R*.

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

Application: 2 µL.

Development: over 2/3 of the plate.

Drying: in air.

(1) This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8. Pharmacopoeial harmonisation*.

Monographs L-P

Detection: spray with *4-aminobenzoic acid solution R* and dry in a current of cold air until the acetone is removed; heat at 100 °C for 15 min, allow to cool then spray with a 2 g/L solution of *sodium periodate R*; dry in a current of cold air and heat at 100 °C for 15 min.

System suitability: reference solution (b):

- the chromatogram shows 2 clearly separated spots.

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

TESTS

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

Dissolve 5.0 g in *water R* and dilute to 50 mL with the same solvent.

Conductivity (*2.2.38*): maximum 20 $\mu S \cdot cm^{-1}$.

Dissolve 20.0 g in *carbon dioxide-free water R* prepared from *distilled water R* by heating at 40-50 °C and dilute to 100.0 mL with the same solvent. After cooling, measure the conductivity of the solution while gently stirring with a magnetic stirrer.

Melting point (*2.2.14*): 165 °C to 170 °C.

Reducing sugars: maximum 0.1 per cent (calculated as glucose equivalent).

To 7.0 g add 13 mL of *water R*. Boil gently with 40 mL of *cupri-tartaric solution R* for 3 min, and allow to stand for 2 min. A precipitate is formed. Filter through a sintered-glass filter (16) (*2.1.2*) coated with *diatomaceous earth R* or a sintered-glass filter (10) (*2.1.2*). Wash the precipitate with hot *water R* (about 50-60 °C) until the washing is no longer alkaline, and filter the washings through the same sintered-glass filter. Discard the filtrate. Immediately dissolve the precipitate in 20 mL of *ferric sulfate solution R*, filter through the same sintered-glass filter, and wash the filter with 15-20 mL of *water R*. Combine the washings and the filtrate, heat to 80 °C, and titrate with *0.02 M potassium permanganate*. Not more than 3.2 mL is required to change the colour of the solution from green to pink so that the colour persists for at least 10 s.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.50 g of the substance to be examined in 2.5 mL of *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (a). Dissolve 0.50 g of *mannitol CRS* in 2.5 mL of *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (b). Dilute 2.0 mL of the test solution to 100.0 mL with *water R*.

Reference solution (c). Dilute 0.5 mL of reference solution (b) to 20.0 mL with *water R*.

Reference solution (d). Dissolve 0.25 g of *mannitol R* and 0.25 g of *sorbitol R* (impurity A) in 5 mL of *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (e). Dissolve 0.5 g of *maltitol R* (impurity B) and 0.5 g of *isomalt R* (impurity C) in 5 mL of *water R* and dilute to 100 mL with the same solvent. Dilute 2 mL of the solution to 10 mL with *water R*.

Column:

- *size*: *l* = 0.3 m, Ø = 7.8 mm;
- *stationary phase*: *strong cation-exchange resin (calcium form) R* (9 µm);
- *temperature*: 85 ± 2 °C.

Mobile phase: degassed *water R*.

Flow rate: 0.5 mL/min.

Detection: refractometer maintained at a constant temperature (40 °C for example).

Injection: 20 µL of the test solution and reference solutions (b), (c), (d) and (e).

Run time: 1.5 times the retention time of mannitol.

Identification of impurities: use the chromatogram obtained with reference solution (d) to identify the peak due to impurity A and the chromatogram obtained with reference solution (e) to identify the peaks due to impurities B and C.

Relative retention with reference to mannitol (retention time = about 20 min): impurity C (1st peak) = about 0.6; impurity B = about 0.7; impurity C (2nd peak) = about 0.73; impurity A = about 1.2. Impurity C elutes in 2 peaks. Coelution of impurity B and the 2nd peak due to impurity C may be observed.

System suitability: reference solution (d):

- *resolution*: minimum 2.0 between the peaks due to mannitol and impurity A.

Limits:

- *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);
- *sum of impurities B and C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);
- *unspecified impurities*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);
- *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);
- *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Nickel (*2.4.15*): maximum 1 ppm.

Suspend 10.0 g in 30.0 mL of *dilute acetic acid R* and dilute to 100.0 mL with *water R*. Use water-saturated *methyl isobutyl ketone R*.

Between each measurement, rinse with *water R* and ensure that the readings return to zero with water-saturated *methyl isobutyl ketone R* treated as described for preparation of the test solution omitting the substance to be examined.

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Microbial contamination. If intended for use in the manufacture of parenteral preparations:

- TAMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

If not intended for use in the manufacture of parenteral preparations:

- TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*);
- TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*);
- absence of *Escherichia coli* (*2.6.13*);
- ◊- absence of *Salmonella* (*2.6.13*).◊

♦**Bacterial endotoxins** (*2.6.14*). If intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins:

- less than 4 IU/g for parenteral preparations having a concentration of 100 g/L or less of mannitol;
- less than 2.5 IU/g for parenteral preparations having a concentration of more than 100 g/L of mannitol.♦

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection: test solution and reference solution (a).

Calculate the percentage content of D-mannitol taking into account the assigned content of *mannitol CRS*.

Monographs L-P

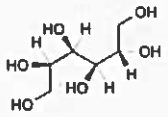
LABELLING

The label states:

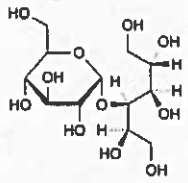
- where applicable, the maximum concentration of bacterial endotoxins;
- where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

IMPURITIES

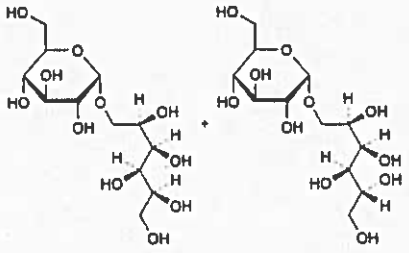
Specified impurities: A, B, C.



A. D-glucitol (D-sorbitol), .



B. 4-*O*-α-D-glucopyranosyl-D-glucitol (D-maltitol),



C. mixture of 6-*O*-α-D-glucopyranosyl-D-glucitol and 1-*O*-α-D-glucopyranosyl-D-mannitol (isomalt).

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for mannitol used as filler in tablets and capsules.

Particle-size distribution (*2.9.31* or *2.9.38*).

Powder flow (*2.9.36*).

01/2017:1674
corrected 9.2

MESNA

Mesnum

$C_2H_5NaO_3S_2$ M_r 164.2
[19767-45-4]

DEFINITION

Sodium 2-sulfanylethanesulfonate.

Content: 96.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance: white or slightly yellow, crystalline powder, hygroscopic.

Solubility: freely soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in cyclohexane.

IDENTIFICATION

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

B. It gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S. Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 50 mL with the same solvent.

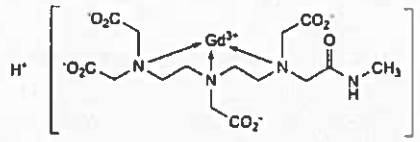
Appearance of solution. Solution S is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

pH (*2.2.3*): 4.5 to 6.0.
Dilute 10 mL of solution S to 20 mL with *carbon dioxide-free water R.*

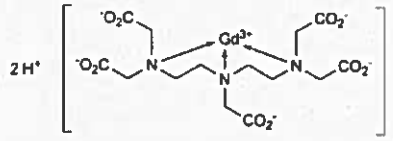
Related substances. Liquid chromatography (*2.2.29*).
Test solution. Dissolve 0.10 g of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.
Reference solution (a). Dissolve 4.0 mg of *mesna impurity C CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 2.0 mL of the solution to 20.0 mL with the mobile phase.
Reference solution (b). Dissolve 6.0 mg of *mesna impurity D CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.
Reference solution (c). Dilute 3.0 mL of the test solution to 10.0 mL with the mobile phase.
Reference solution (d). Dilute 1.0 mL of reference solution (c) to 100.0 mL with the mobile phase.
Reference solution (e). Dilute 6.0 mL of reference solution (c) to 20.0 mL with the mobile phase. To 10 mL of the solution add 10 mL of reference solution (a).
Column:
- *size*: *l* = 0.25 m, Ø = 4.6 mm,
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (10 µm).

Mobile phase: dissolve 2.94 g of *potassium dihydrogen phosphate R*, 2.94 g of *dipotassium hydrogen phosphate R* and 2.6 g of *tetrabutylammonium hydrogen sulfate R* in about 600 mL of *water R*. Adjust to pH 2.3 with *phosphoric acid R*, add 335 mL of *methanol R* and dilute to 1000 mL with *water R*.
Flow rate: 1 mL/min.
Detection: spectrophotometer at 235 nm.

Monographs L P



A. hydrogen[3,6-bis(carboxylatomethyl)-9-[(methylcarbamoyl)methyl]-3,6,9-triazaundecanedioato-κ^3N^3,N^6,N^9-gadolinate](1-) (Gd-DTPA-MMA),



B. dihydrogen[3,6,9-tris(carboxylatomethyl)-3,6,9-triazaundecanedioato-κ^3N^3,N^6,N^9-gadolinate](2-) (Gd-DTPA),

C. $H_3C\text{-}NH_2$: methanamine (methylamine).

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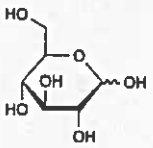
corrected 9.1

GLUCOSE(1)

Glucosum



$C_6H_{12}O_6$ M_r 180.2
[50-99-7]

DEFINITION

D-Glucopyranose.

It is derived from starch.

Content: 97.5 per cent to 102.0 per cent (anhydrous substance).

♦CHARACTERS

Appearance: white or almost white, crystalline powder.

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

IDENTIFICATION

First identification: ◊A◊, *B, E.*

◊*Second identification*: *C, D.*◊

◊A. Specific optical rotation (*2.2.7*): + 52.5 to + 53.3 (anhydrous substance).

Dissolve 10.0 g in 80 mL of *water R*, add 0.2 mL of *dilute ammonia R1*, allow to stand for 30 min and dilute to 100.0 mL with *water R*.◊

B. Examine the chromatograms obtained in the assay.

Results: the principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

◊C. Thin-layer chromatography (*2.2.27*).

Solvent mixture: *water R*, *methanol R* (2:3 *V/V*).

Test solution. Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 20 mL with the solvent mixture.

Reference solution (a). Dissolve 10 mg of *glucose monohydrate CRS* in the solvent mixture and dilute to 20 mL with the solvent mixture.

Reference solution (b). Dissolve 10 mg each of *fructose R*, *glucose R*, *lactose monohydrate R* and *sucrose R* in the solvent mixture and dilute to 20 mL with the solvent mixture.

Plate: *TLC silica gel plate R.*

Mobile phase: *water R*, *methanol R*, *anhydrous acetic acid R*, *ethylene chloride R* (10:15:25:50 *V/V/V/V*); measure the volumes accurately since a slight excess of water produces cloudiness.

Application: 2 µL; thoroughly dry the points of application.

Development A: over 3/4 of the plate.

Drying A: in a current of warm air.

Development B: immediately, over 3/4 of the plate, after renewing the mobile phase.

Drying B: in a current of warm air.

Detection: treat with a solution of 0.5 g of *thymol R* in a mixture of 5 mL of *sulfuric acid R* and 95 mL of *ethanol (96 per cent) R*; heat at 130 °C for 10 min.

System suitability: reference solution (b):

– the chromatogram shows 4 clearly separated spots.

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

D. Dissolve 0.1 g in 10 mL of *water R*. Add 3 mL of *cupri-tartaric solution R* and heat. A red precipitate is formed.◊

E. Water (see Tests).

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_7 (*2.2.2, Method II*).

Dissolve 10.0 g in 15 mL of *water R*, heating on a water-bath.

Conductivity (*2.2.38*): maximum 20 µS·cm^{-1}.

Dissolve 20.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100.0 mL with the same solvent. Measure the conductivity of the solution while gently stirring with a magnetic stirrer.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.300 g of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (a). Dissolve 0.330 g of *glucose monohydrate CRS* in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (b). Dilute 1.0 mL of the test solution to 250.0 mL with *water R*.

Reference solution (c). Dilute 25.0 mL of reference solution (b) to 200.0 mL with *water R*.

Reference solution (d). Dissolve 5 mg of *fructose R* (impurity D), 5 mg of *maltose monohydrate R* (impurity A) and 5 mg of *maltotriose R* (impurity C) in *water R* and dilute to 50 mL with the same solvent.

Column:

– *size*: *l* = 0.3 m, Ø = 7.8 mm;

– *stationary phase*: *strong cation-exchange resin (calcium form) R* (9 µm);

– *temperature*: 85 ± 1 °C.

Mobile phase: degassed *water R*.

Flow rate: 0.3 mL/min.

Detection: refractometer maintained at a constant temperature (40 °C for example).

(1) This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

Injection: 20 µL of the test solution and reference solutions (b), (c) and (d).

Run time: 1.5 times the retention time of glucose.

Relative retention with reference to glucose (retention time = about 21 min): impurity C = about 0.7; impurities A and B = about 0.8; impurity D = about 1.3.

System suitability: reference solution (d):

- *resolution*: minimum 1.3 between the peaks due to impurities C and A.

Limits:

- *sum of impurities A and B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent);
- *impurity C*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);
- *impurity D*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.15 per cent);
- *unspecified impurities*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);
- *total*: not more than 1.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);
- *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Dextrin. To 1 g of the finely powdered substance to be examined add 20 mL of *ethanol (96 per cent) R* and heat under a reflux condenser. The substance dissolves completely.

Soluble starch, sulfite: maximum 15 ppm.

Dissolve 6.7 g in 15.0 mL of *water R*, heating on a water-bath. Allow to cool and add 25 µL of *iodine solution R5*. The solution is yellow.

Water (*2.5.12*): maximum 1.0 per cent, determined on 0.50 g.

◊**Pyrogens** (*2.6.8*). If intended for use in the manufacture of large-volume parental preparations without a further appropriate procedure for the removal of pyrogens, 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 solution in *water for injections R* containing 50 mg of the substance to be examined per millilitre.◊

ASSAY

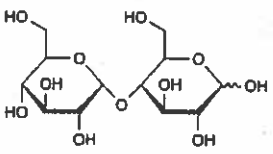
Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection: test solution and reference solution (a).

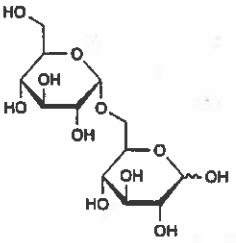
Calculate the percentage content of $C_6H_{12}O_6$ taking into account the assigned content of *glucose monohydrate CRS*.

IMPURITIES

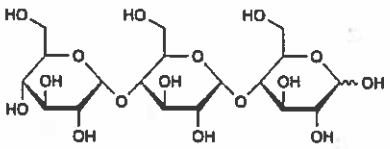
Specified impurities: A, B, C, D.



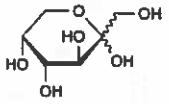
A. 4-*O*-α-D-glucopyranosyl-D-glucopyranose (maltose),



B. 6-*O*-α-D-glucopyranosyl-D-glucopyranose (isomaltose),



C. α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-D-glucopyranose (maltotriose),



D. D-*arabino*-hex-2-ulopyranose (fructose).

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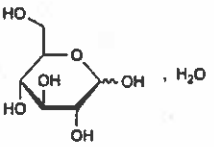
corrected 9.1

GLUCOSE MONOHYDRATE[2]

Glucosum monohydricum



$C_6H_{12}O_6,H_2O$ M_r 198.2
[77938-63-7]

DEFINITION

D-Glucopyranose monohydrate.

It is derived from starch.

Content: 97.5 per cent to 102.0 per cent (anhydrous substance).

♦CHARACTERS

Appearance: white or almost white, crystalline powder.

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

IDENTIFICATION

First identification: ◊A◊, *B, E.*

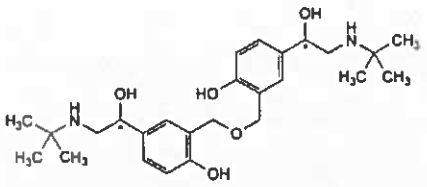
◊*Second identification*: *C, D.*◊

◊A. Specific optical rotation (*2.2.7*): + 52.5 to + 53.3 (anhydrous substance).

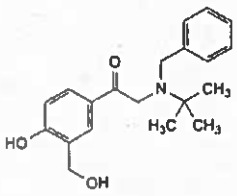
Dissolve 10.0 g in 80 mL of *water R*, add 0.2 mL of *dilute ammonia R1*, allow to stand for 30 min and dilute to 100.0 mL with *water R*.◊

B. Examine the chromatograms obtained in the assay.

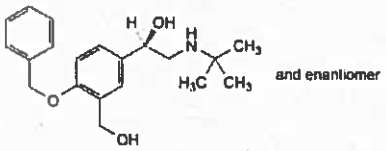
(2) This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.



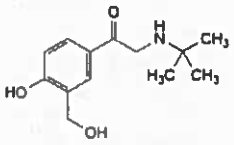
F. 1,1'-[oxybis[methylene(4-hydroxy-1,3-phenylene)]]bis[2-[(1,1-dimethylethyl)amino]ethanol],



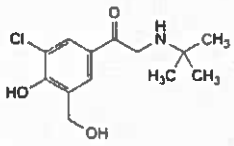
G. 2-[benzyl(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanone,



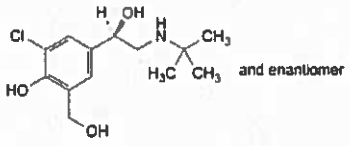
I. (1*RS*)-2-[(1,1-dimethylethyl)amino]-1-[4-(benzyloxy)-3-(hydroxymethyl)phenyl]ethanol,



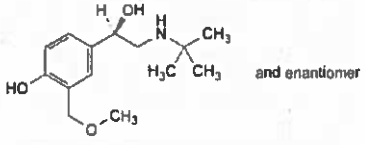
J. 2-[(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanone (salbutamone),



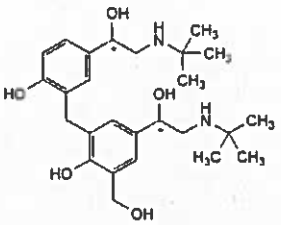
K. 2-[(1,1-dimethylethyl)amino]-1-[3-chloro-4-hydroxy-5-(hydroxymethyl)phenyl]ethanone,



L. (1*RS*)-2-[(1,1-dimethylethyl)amino]-1-[3-chloro-4-hydroxy-5-(hydroxymethyl)phenyl]ethanol,



M. (1*RS*)-2-[(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(methoxymethyl)phenyl]ethanol,



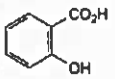
N. 2-[(1,1-dimethylethyl)amino]-1-[3-[[5-[2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-2-hydroxyphenyl]methyl]-4-hydroxy-5-(hydroxymethyl)phenyl]ethanol,

O. unknown structure.

01/2017:0366

SALICYLIC ACID

Acidum salicylicum



$C_7H_6O_3$ M_r 138.1
[69-72-7]

DEFINITION

2-Hydroxybenzenecarboxylic acid.

Content: 99.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

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

Solubility: slightly soluble in water, freely soluble in ethanol (96 per cent), sparingly soluble in methylene chloride.

IDENTIFICATION

First identification: A, B.

Second identification: A, C.

A. Melting point (2.2.14): 158 °C to 161 °C.

B. Infrared absorption spectrophotometry (2.2.24).
Comparison: *salicylic acid CRS*.

C. Dissolve about 30 mg in 5 mL of *0.05 M sodium hydroxide*, neutralise if necessary and dilute to 20 mL with *water R*. 1 mL of the solution gives reaction (a) of salicylates (2.3.1).

TESTS

Solution S. Dissolve 2.5 g in 50 mL of boiling *distilled water R*, cool and filter.

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

Dissolve 1 g in 10 mL of *ethanol (96 per cent) R*.

Related substances. Liquid chromatography (2.2.29).

Test solution. Dissolve 0.50 g of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a). Dissolve 10 mg of *phenol R* (impurity C) in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (b). Dissolve 5 mg of *salicylic acid impurity B CRS* in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (c). Dissolve 50 mg of *4-hydroxybenzoic acid R* (impurity A) in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (d). Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase.

Reference solution (e). Dilute a mixture of 1.0 mL of each of reference solutions (a), (b) and (c) to 10.0 mL with the mobile phase.

Reference solution (f). Dilute a mixture of 0.1 mL of each of reference solutions (a), (b) and (c) to 10.0 mL with the mobile phase.

Column:

- *size*: *l* = 0.15 m, Ø = 4.6 mm;
- *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: *glacial acetic acid R, methanol R, water R* (1:40:60 *V/V/V*).

Flow rate: 0.5 mL/min.

Detection: spectrophotometer at 270 nm.

Injection: 10 µL of the test solution and reference solutions (d), (e) and (f).

Identification of impurities: use the chromatogram obtained with reference solution (e) to identify the peaks due to impurities A, B and C.

Relative retention with reference to impurity C (retention time = about 9.5 min): impurity A = about 0.6; impurity B = about 0.8.

System suitability: reference solution (e):

- the 3rd peak in the chromatogram corresponds to the peak due to impurity C in the chromatogram obtained with reference solution (d);
- *resolution*: minimum 1.0 between the peaks due to impurities B and C; if necessary, adjust the quantity of acetic acid in the mobile phase.

Limits:

- *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.1 per cent);
- *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.05 per cent);
- *impurity C*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.02 per cent);
- *unspecified impurities*: for each impurity, not more than the area of the peak due to impurity B in the chromatogram obtained with reference solution (f) (0.05 per cent);
- *total*: not more than twice the area of the peak due to impurity A in the chromatogram obtained with reference solution (f) (0.2 per cent);
- *disregard limit*: 0.3 times the area of the peak due to impurity A in the chromatogram obtained with reference solution (f) (0.03 per cent). Do not disregard the peak due to impurity C.

Chlorides (*2.4.4*): maximum 100 ppm.

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

Sulfates: maximum 200 ppm.

Dissolve 1.0 g in 5 mL of *dimethylformamide R* and add 4 mL of *water R*. Mix thoroughly. Add 0.2 mL of *dilute hydrochloric acid R* and 0.5 mL of a 25 per cent *m/m* solution of *barium chloride R*. After 15 min any opalescence in the solution is not more intense than that in a standard prepared as follows: to 2 mL of *sulfate standard solution (100 ppm SO_4) R* add 0.2 mL of *dilute hydrochloric acid R*, 0.5 mL of a 25 per cent *m/m* solution of *barium chloride R*, 3 mL of *water R* and 5 mL of *dimethylformamide R*.

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in a desiccator.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 2.0 g.

ASSAY

Dissolve 0.120 g in 30 mL of *ethanol (96 per cent) R* and add 20 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, using 0.1 mL of *phenol red solution R* as indicator.

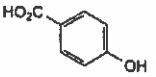
1 mL of *0.1 M sodium hydroxide* is equivalent to 13.81 mg of $C_7H_6O_3$.

STORAGE

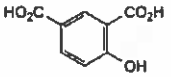
Protected from light.

IMPURITIES

Specified impurities: *A, B, C.*



A. 4-hydroxybenzoic acid,



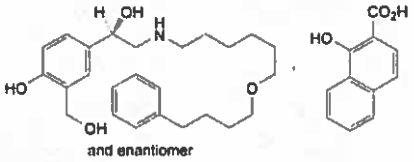
B. 4-hydroxyisophthalic acid,

C. phenol.

04/2014:1765

SALMETEROL XINAFOATE

Salmeteroli xinafoas



and enantiomer

$C_{36}H_{45}NO_7$ M_r 604

[94749-08-3]

DEFINITION

(1*RS*)-1-[4-Hydroxy-3-(hydroxymethyl)phenyl]-2-[[6-(4-phenylbutoxy)hexyl]amino]ethanol 1-hydroxynaphthalene-2-carboxylate.

Content: 97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

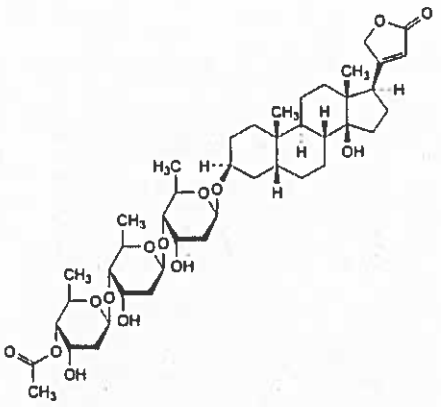
Appearance: white or almost white powder.

Solubility: practically insoluble in water, soluble in methanol, slightly soluble in anhydrous ethanol, practically insoluble in methylene chloride.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *salmeterol xinafoate CRS*.

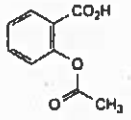


H. 3β-[(4-*O*-acetyl-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-14-hydroxy-5β-card-20(22)-enolide (β-acetyldigitoxin).

01/2017:0309

ACETYLSALICYLIC ACID

Acidum acetylsalicylicum



$C_9H_8O_4$ M_r 180.2
[50-78-2]

DEFINITION

2-(Acetyloxy)benzoic acid.

Content: 99.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

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

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

mp: about 143 °C (instantaneous method).

IDENTIFICATION

First identification: *A, B.*

Second identification: *B, C, D.*

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *acetylsalicylic acid CRS.*

B. To 0.2 g add 4 mL of *dilute sodium hydroxide solution R* and boil for 3 min. Cool and add 5 mL of *dilute sulfuric acid R*. A crystalline precipitate is formed. Filter, wash the precipitate and dry at 100-105 °C. The melting point (*2.2.14*) is 156 °C to 161 °C.

C. In a test tube mix 0.1 g with 0.5 g of *calcium hydroxide R*. Heat the mixture and expose to the fumes produced a piece of filter paper impregnated with 0.05 mL of *nitrobenzaldehyde solution R*. A greenish-blue or greenish-yellow colour develops on the paper. Moisten the paper with *dilute hydrochloric acid R*. The colour becomes blue.

D. Dissolve with heating about 20 mg of the precipitate obtained in identification test B in 10 mL of *water R* and cool. The solution gives reaction (a) of salicylates (*2.3.1*).

TESTS

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

Dissolve 1.0 g in 9 mL of *ethanol (96 per cent) R*.

Related substances. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution. Dissolve 0.100 g of the substance to be examined in *acetonitrile for chromatography R* and dilute to 10.0 mL with the same solvent.

Reference solution (a). Dissolve 50.0 mg of *salicylic acid R* (impurity C) in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (b). Dissolve 10 mg of *salicylic acid R* (impurity C) in the mobile phase and dilute to 10.0 mL with the mobile phase. To 1.0 mL of the solution add 0.2 mL of the test solution and dilute to 100.0 mL with the mobile phase.

Reference solution (c). Dissolve with the aid of ultrasound the contents of a vial of *acetylsalicylic acid for peak identification CRS* (containing impurities A, B, D, E and F) in 1.0 mL of *acetonitrile R*.

Column:
- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: *phosphoric acid R, acetonitrile for chromatography R, water R* (2.400:600 *V/V/V*).

Flow rate: 1 mL/min.

Detection: spectrophotometer at 237 nm.

Injection: 10 µL.

Run time: 7 times the retention time of acetylsalicylic acid.

Identification of impurities: use the chromatogram obtained with reference solution (a) to identify the peak due to impurity C; use the chromatogram supplied with *acetylsalicylic acid for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, D, E and F.

Relative retention with reference to acetylsalicylic acid (retention time = about 5 min): impurity A = about 0.7; impurity B = about 0.8; impurity C = about 1.3; impurity D = about 2.3; impurity E = about 3.2; impurity F = about 6.0.

System suitability: reference solution (b):
- *resolution*: minimum 6.0 between the peaks due to acetylsalicylic acid and impurity C.

Limits:
- *impurities A, B, C, D, E, F*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);
- *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);
- *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.25 per cent);
- *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent).

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo*.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

In a flask with a ground-glass stopper, dissolve 1.000 g in 10 mL of *ethanol (96 per cent) R*. Add 50.0 mL of *0.5 M sodium hydroxide*. Close the flask and allow to stand for 1 h. Using 0.2 mL of *phenolphthalein solution R* as indicator, titrate with *0.5 M hydrochloric acid*. Carry out a blank titration.

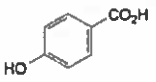
1 mL of *0.5 M sodium hydroxide* is equivalent to 45.04 mg of $C_9H_8O_4$.

STORAGE

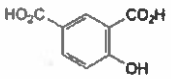
In an airtight container.

IMPURITIES

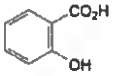
Specified impurities: A, B, C, D, E, F.



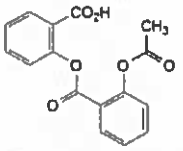
A. 4-hydroxybenzoic acid,



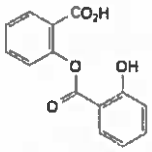
B. 4-hydroxybenzene-1,3-dicarboxylic acid (4-hydroxyisophthalic acid),



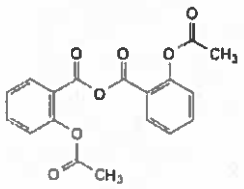
C. 2-hydroxybenzenecarboxylic acid (salicylic acid),



D. 2-[[2-(acetyloxy)benzoyl]oxy]benzoic acid (acetylsalicylsalicylic acid),



E. 2-[(2-hydroxybenzoyl)oxy]benzoic acid (salsalate, salicylsalicylic acid),

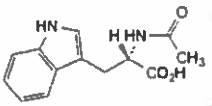


F. 2-(acetyloxy)benzoic anhydride (acetylsalicylic anhydride).

01/2017:1383

N-ACETYLTRYPTOPHAN

N-Acetyltryptophanum



and enantiomer

$C_{13}H_{14}N_2O_3$ M_r 246.3

[87-32-1]

DEFINITION

(*RS*)-2-Acetylamino-3-(1*H*-indol-3-yl)propanoic acid.

Content: 99.0 per cent to 101.0 per cent (dried substance).

PRODUCTION

Tryptophan used for the production of *N*-acetyltryptophan complies with the test for impurity A and other related substances in the monograph on *Tryptophan (1272)*.

CHARACTERS

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

Solubility: slightly soluble in water, very soluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

mp: about 205 °C.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D, E.

A. Optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *N-acetyltryptophan CRS*.

C. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 50 mg of the substance to be examined in 0.2 mL of *concentrated ammonia R* and dilute to 10 mL with *water R*.

Reference solution (a). Dissolve 50 mg of *N-acetyltryptophan CRS* in 0.2 mL of *concentrated ammonia R* and dilute to 10 mL with *water R*.

Reference solution (b). Dissolve 10 mg of *tryptophan R* in the test solution and dilute to 2 mL with the test solution.

Plate: *TLC silica gel F_{254} plate R*.

Mobile phase: *glacial acetic acid R, water R, butanol R* (25:25:40 *V/V/V*).

Application: 2 µL.

Development: over a path of 10 cm.

Drying: in an oven at 100-105 °C for 15 min.

Detection: examine in ultraviolet light at 254 nm.

System suitability: reference solution (b):

- the chromatogram shows 2 clearly separated spots.

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

D. Dissolve about 2 mg in 2 mL of *water R*. Add 2 mL of *dimethylaminobenzaldehyde solution R6*. Heat on a water-bath. A blue or greenish-blue colour develops.

E. It gives the reaction of acetyl (*2.3.1*). Proceed as described for substances hydrolysable only with difficulty.

ESAME DI STATO PER L'ABILITAZIONE ALL'ESERCIZIO DELLA PROFESSIONE DI FARMACISTA

I SESSIONE 2017

PROVA PRATICA: SPEDIZIONE DELLA RICETTA

Il candidato riceve in allegato un fac-simile di ricetta.
Il candidato dovrà provvedere alla tariffazione, alla compilazione della etichetta e a rispondere ad un breve questionario inerente alla tipologia della ricetta.

Cognome e nome…….. N° Ricetta…

Dott. XXXX XXXXX
Medico Chirurgo
Via XXXXX, 12 – XXXXX

Sig. XXXX XXXXXXX

R/ Acido acetilsalicilico	2,70 g
Sodio benzoato	0,70 g
Acido ascorbico	0,60 g
Lattosio	1,20 g

Dividi in XV cialdini

S/ 3 cialdini al di'

Torino, 30.6.2017

XXXXX XXXXXX

ESAME DI STATO PER L'ABILITAZIONE ALL'ESERCIZIO DELLA PROFESSIONE DI FARMACISTA

I SESSIONE 2017

n°……li……Dott……..… **……** **……** **……** **……** **……** **……** **……** **……** **……** **Avvertenze……..……** **……** **……** **Precauzioni……..…** **……** **……** **Posologia……..…** **……** **……** **Data limite di utilizzo……** **Sig……..…**	

Cognome e Nome _____Prova n°_____

Scheda ricetta

Tipologia

□ RR □ RNR □ RNR (tab 3) □ RRM □ SSN

La ricetta risulta spedibile?

□ si

□ no perché?

Validità temporale ed eventuale ripetibilità della ricetta in oggetto:

Formalismi obbligatori per il **medico** per la ricetta in oggetto:

Formalismi obbligatori per il **farmacista** per la ricetta in oggetto:

Presenza di:

□ veleni, sostanze tossiche
□ sost. stupefacenti e psicotrope
□ coloranti o corrosivi
□ sostanze vietate per doping
□ registrazione registro EU

Modalità e tempo di conservazione della ricetta

Data limite di utilizzo della preparazione

Uso
□ UI □ UE

Forma farmaceutica

Controllo di qualità obbligatori per le NBP:

Attività terapeutica della preparazione

SCADENZA MATERIE PRIME

ACIDO ACETILSALICILICO	30 giugno 2019
LATTOSIO	31 marzo 2018
SODIO BENZOATO	31 dicembre 2018
ACIDO ASCORBICO	30 giugno 2018

TABELLA N. 8

Dosi dei medicinali per l'adulto, oltre le quali il farmacista non può fare la spedizione, salvo il caso di dichiarazione speciale del medico (art. 34, comma 3 e art. 40 del Regolamento per il Servizio Farmaceutico approvato con R.D. 30 settembre 1938, n. 1706).

(Il controllo delle dosi e la conseguente dichiarazione in caso di iperdosaggio è riferibile ai preparati estemporanei e non ai medicinali di origine industriale per i quali la "sicurezza del dosaggio", anche in relazione agli eventuali limiti stabiliti per le sostanze correlate, è stata accertata in sede di registrazione dall'Autorità competente.)

** Le sostanze contrassegnate con un asterisco hanno, nella sezione NOTE, alcune informazioni supplementari. Per facilitare la consultazione di tale sezione, l'elenco delle sostanze viene presentato in ordine alfabetico.*

Sostanza	Vie di somministrazione	Dosi abituali		Dosi massime	
		Per ogni dose grammi	Nelle 24 ore grammi	Per ogni dose grammi	Nelle 24 ore grammi
Acamprosato calcico *	per os	–	–	–	1,33
Acebutololo cloridrato	per os	0,1-0,2	0,4	0,4	1,2
Aceclofenac	per os	–	–	–	0,100
Acetazolamide	per os i.m. o e.v.	0,25 0,25	0,75 0,50	0,50 0,50	1 1
Acetilcisteina	per os sol. al. (20-10%) per aerosol e.v. lenta (g/kg) (Intossicazione da paracetamolo)	0,2-0,4 0,4 1,0 0,07-0,15	1,0 4,0 –	1,0 0,2-2 –	1,0 10 0,3
Acetilcolina cloruro	top. (oft.)	–	–	0,5-2 ml di una soluzione fresca 1%	
Acetildiidrocodeina (come base anidra)	per os	0,01-0,02	0,06	0,06	0,180
Aciclovir	e.v. lenta per os top. 3-5%	0,35 0,2-0,4 –	1,0 1,0 –	0,7 0,8 –	2,0 4,0 –
Acido acetilsalicilico *	per os	0,5	1-2	1	6
Acido amidotrizoico (come Iodio)	e.v. lenta	–	20	–	1/kg
Acido amminocaproico	e.v. lenta per os	4-5 2-4	8-10 16	6	30 30
Acido ascorbico	per os o s.c. o i.m. e.v.	0,10-0,50 0,50-1	0,50-1 0,50-1	– –	– –
Acido chenodesossicolico	per os	–	–	–	0,0175/kg
Acido deidrocolico	per os	0,25	0,75	0,50	1,50
Acido etacrinico *	per os infusione e.v.	–	–	0,050	0,150 0,050
Acido folico	per os i.m.	0,005 0,005	0,02 0,01	0,01 0,01	0,05 0,02
Acido fusidico	top. per os (ad.) per os (ped. < 1 a.) idem (1-5 a.)	pom. ung. cr. o gel 0,2% 0,5 0,015 0,25	2 v. 1,5 0,05 0,75	idem 1 0,03 0,5	3-4 v. 1,5 0,075 1
Acido glutammico	per os	0,3	0,6	0,6	1,8
Acido iopanoico *	per os	1,0-3,0	2,0-6,0	3	6
Acido iotalamico	e.v. lenta	Sol. al 70% di sale sodico o al 60% di sale di meglumina o di miscela dei due			
Acido ioxaglico *	e.v.	–	–	5ml/kg	5ml/kg