**647510** **MSC3AnaC302x** **Seat No :_____**

# M.Sc.(Chem.) Semester - 3 (*CBCS*) Examination
## Nov/Dec-2023 (NEW COURSE)
## Pharma Regulatory Affairs (Core(New))

**Time: 2:30 Hours** **Marks: 70**

**Instructions:**

1. All questions are compulsory.
2. Figures to the right indicate marks.

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Que.1(A) Answer the following question. (04)

1. What is SOP of SOP? Briefly explain various elements of SOP.

Que.1(B) Answer any two questions out of three. (10)

1. Prepare Standard specification of Tolfenamic Acid from given official EU monograph. (See Annexure 1)
2. Define documentation, briefly explain its purpose and give few examples of important document in pharmaceutical manufacturing.
3. Write SOP for operation and calibration of digital Polarimeter.

Que.2(A) Answer the following question. (04)

1. Explain static document and dynamic document in brief.
2. State an objectives of instrument qualification.

Que.2(B) Answer any two questions out of three. (10)

1. Define the term qualification and draw the qualification chart.
2. When dose the qualification of analyst shall be done? Which types of capabilities should be covered under analyst qualification?
3. Give an account of performance qualification and briefly distinguish between performance qualification and operational qualification.

Que.3(A) Answer the following question. (04)

1. Draw master calibration schedule for QC lab.
   (12 months chart including minimum 10 instruments or equipments)

Que.3(B) Answer any two questions out of three. (10)

1. Write the calibration process for following:
   (A) TDS meter (B) Abbe refrecto meter
2. Define calibration and give brief introduction, when measuring instrument should be calibrated as per GMP.
3. Find the % recovery from following accuracy study data
   Standard concentration = 100 ppm, Mean area of standard = 5000;

| % Level | Set | Mean Area | Amount Added (mg) | Amount Found (mg) | % recovery |
|---|---|---|---|---|---|
| 50 | 1 | 2499 | 5.01 | | |
| | 2 | 2500 | 5.00 | | |
| | 3 | 2510 | 5.05 | | |
| 100 | 1 | 5015 | 10.00 | | |
| | 2 | 5050 | 10.12 | | |
| | 3 | 5009 | 09.97 | | |
| 150 | 1 | 7487 | 14.86 | | |
| | 2 | 7499 | 14.92 | | |
| | 3 | 7515 | 14.98 | | |

Que.4(A) Answer the following question. (04)

1. Write an objectives of stability studies.
2. Prepare table for various zones and its climate as per ICH guideline.

Que.4(B) Answer any two questions out of three. (10)

1. Explain stress test for APIs in detailed.
2. Discuss about selection of samples and testing frequencies for stability studies.
3. Prepare storage conditions table for (i) General case (ii) Storage under refrigeration (iii) Storage in freezer.

Que.5(A) Answer the following question. (04)

1. What is quality? Who are responsible to maintain the quality?
2. What is GLP? Note down major components covered under GLP.

Que.5(B) Answer any two questions out of three. (10)

1. Write a note on fundamental needs in terms of calibration and validation as per GLP.
2. Discuss minimum requirements for personal under GLP.
3. Give the examples of violation of GLP practices in following criteria
   (A) Equipment (B) Building and premises

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# ANNEXURE 1

– *teicoplanin $A_3$ group*: 4.0 per cent to 12.0 per cent;
– *teicoplanin $A_{2\text{-}3}$*: 4.0 per cent to 8.5 per cent;
– *teicoplanin $A_{2\text{-}1}$*: 2.0 per cent to 7.0 per cent;
– *teicoplanin $A_{2\text{-}1a}$*: 0.5 per cent to 5.5 per cent;
– *teicoplanin $A_{2\text{-}1b}$*: 0.5 per cent to 4.0 per cent;
– *teicoplanin $A_{2\text{-}6}$ group*: maximum 5.0 per cent;
– *disregard limit*: 0.25 per cent.

**Related substances**. Liquid chromatography (*2.2.29*) as described in the test for composition. Use the normalisation procedure.

Use the chromatogram obtained with reference solution (a) to identify all peaks present above the disregard limit as teicoplanin-like related substances. Any peak present in any part of the chromatogram obtained with the test solution that cannot be correlated to a peak above the disregard limit in reference solution (a) should be considered as a non-teicoplanin-like impurity, unless it is characterized by other means.

A teicoplanin-like related substance is defined as a substance that shares the same glycopeptide core structure of the parent molecule, composed of a linear heptapeptide aglycone, an α-D-mannose and an acetyl-β-D-glucosamine.

The R′ side chains in the teicoplanin-like related substances RS $A_{2\text{-}6a}$, RS $A_{2\text{-}6b}$ and RS $A_{2\text{-}6c}$ are unknown.

Calculate the percentage contents using the following equations:

$$\text{teicoplanin-like related substance (x)} = \frac{A_{\mathrm{RSTLx}}}{(\mathrm{S2} + 0.83 \times \mathrm{S_3})} \times 100$$

$A_{\mathrm{RSTLx}}$ = area of the peak due to the teicoplanin-like related substance (x) in the chromatogram obtained with the test solution;

$$\text{non-teicoplanin-like impurity (x)} = \frac{A_{\mathrm{Ix}}}{(\mathrm{S2} + 0.83 \times \mathrm{S_3})} \times 100$$

$A_{\mathrm{Ix}}$ = area of the peak due to the non-teicoplanin-like impurity (x) in the chromatogram obtained with the test solution.

*Limits*:
– *teicoplanin-like related substance RS $A_{2\text{-}6c}$*: maximum 2.5 per cent;
– *teicoplanin-like related substance RS $A_{2\text{-}6a}$*: maximum 1.5 per cent;
– *teicoplanin-like related substance RS $A_{2\text{-}6b}$*: maximum 1.5 per cent;
– *any non-teicoplanin-like impurity other than impurity A*: maximum 0.5 per cent;
– *total non-teicoplanin-like impurities other than impurity A*: maximum 1.5 per cent.

**Impurity A**. Liquid chromatography (*2.2.29*) as described in the test for composition with the following modifications.

*Injection*: 20 µL of the test solution and reference solution (c).

*Relative retention* with reference to teicoplanin $A_{2\text{-}2}$ (retention time = about 18 min): impurity A = about 0.6.

*Calculation of percentage content*:
– for impurity A, use the concentration of impurity A in reference solution (c).

*Limit*:
– *impurity A*: maximum 0.2 per cent.

**Chlorides**: maximum 5.0 per cent, expressed as sodium chloride (anhydrous substance).

Dissolve 1.000 g in 300 mL of *water R*, stir and acidify with 2 mL of *nitric acid R*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 5.844 mg of NaCl.

**Water** (*2.5.12*): maximum 15.0 per cent, determined on 0.300 g.

ASSAY

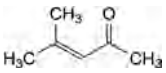
Carry out the microbiological assay of antibiotics (*2.7.2*), using the diffusion method. Use *teicoplanin CRS* as the reference substance.

STORAGE

Protected from light, at a temperature of 2 °C to 8 °C.

IMPURITIES

*Specified impurities: A.*

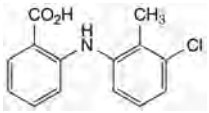


A. 4-methylpent-3-en-2-one (mesityl oxide).

**07/2019:2039**

# TOLFENAMIC ACID

## Acidum tolfenamicum



$C_{14}H_{12}ClNO_2$ $M_r$ 261.7
[13710-19-5]

DEFINITION

2-(3-Chloro-2-methylanilino)benzoic acid.

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

CHARACTERS

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

*Solubility*: practically insoluble in water, soluble in dimethylformamide, sparingly soluble in anhydrous ethanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides.

mp: about 213 °C.

IDENTIFICATION

*First identification: B.*

*Second identification: A, C.*

A. Dissolve 20 mg in a mixture of 1 volume of *1 M hydrochloric acid* and 99 volumes of *methanol R* and dilute to 100 mL with the same mixture of solvents. Dilute 5.0 mL of the solution to 50 mL with a mixture of 1 volume of *1 M hydrochloric acid* and 99 volumes of *methanol R*. Examined between 250 nm and 380 nm (*2.2.25*), the solution shows 2 absorption maxima, at 286 nm and 345 nm. The ratio of the absorbance measured at the maximum at 286 nm to that measured at the maximum at 345 nm is 1.2 to 1.4.

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

C. Thin-layer chromatography (*2.2.27*).
*Test solution*. Dissolve 25 mg of the substance to be examined in a mixture of 1 volume of *methanol R* and 3 volumes of *methylene chloride R* and dilute to 10 mL with the same mixture of solvents.

*Reference solution*. Dissolve 25 mg of *tolfenamic acid CRS* in a mixture of 1 volume of *methanol R* and 3 volumes of *methylene chloride R* and dilute to 10 mL with the same mixture of solvents.

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

*Mobile phase*: *glacial acetic acid R*, *dioxan R*, *toluene R* (1:25:90 *V/V/V*).

*Application*: 10 µL.

*Development*: over 2/3 of the plate.

*Drying*: in a current of warm air.

*Detection*: ultraviolet light at 254 nm.

*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 the reference solution.

TESTS

**Related substances**. Liquid chromatography (*2.2.29*).

*Test solution*. Dissolve 50.0 mg of the substance to be examined in 5 mL of *anhydrous ethanol R* and dilute to 50.0 mL with the mobile phase.

*Reference solution (a)*. Dissolve 25.0 mg of *2-chlorobenzoic acid R* (impurity A) and 25.0 mg of *3-chloro-2-methylaniline R* (impurity B) in 5 mL of *anhydrous ethanol R* and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

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

*Column*:

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

*Mobile phase*: *glacial acetic acid R*, *water for chromatography R*, *anhydrous ethanol R* (0.2:35:65 *V/V/V*).

*Flow rate*: 0.8 mL/min.

*Detection*: spectrophotometer at 232 nm.

*Injection*: 20 µL.

*Run time*: 3 times the retention time of tolfenamic acid.

*Relative retention* with reference to tolfenamic acid (retention time = about 15 min): impurity A = about 0.25; impurity B = about 0.34.

*System suitability*: reference solution (a):

- *resolution*: minimum 2.5 between the peaks due to impurity A and to impurity B.

*Limits*:

- *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
- *impurity B*: not more than half the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.05 per cent);
- *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);
- *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);
- *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.01 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.

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

ASSAY

Dissolve 0.200 g with the aid of ultrasound in 100 mL of *anhydrous ethanol R*. Add 0.1 mL of *phenol red solution R* and titrate with *0.1 M sodium hydroxide*.

1 mL of *0.1 M sodium hydroxide* is equivalent to 26.17 mg of $C_{14}H_{12}ClNO_2$.

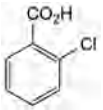
STORAGE

Protected from light.

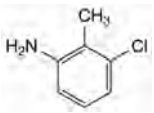
IMPURITIES

*Specified impurities: A, B.*

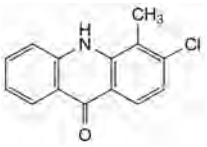
*Other detectable impurities* (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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




A. 2-chlorobenzoic acid,




B. 3-chloro-2-methylaniline,

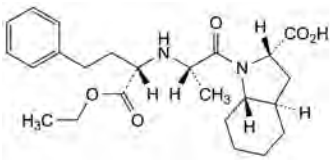



C. 3-chloro-4-methylacridin-9(10*H*)-one.

**07/2019:2245**

# TRANDOLAPRIL

## Trandolaprilum




$C_{24}H_{34}N_2O_5$ $M_r$ 430.5

[87679-37-6]

DEFINITION

(2*S*,3a*R*,7a*S*)-1-[(2*S*)-2-[[(2*S*)-1-Ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid.

*Content*: 99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

*Appearance*: white or almost white powder.

*Solubility*: practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in anhydrous ethanol.