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Diclofenac Diethylamine

Details for the public consultation of this monograph are as follows:

EAG/Panel/Working Party	Medicinal Chemicals 2
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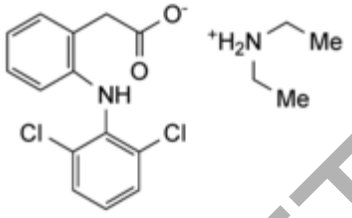
Deadline for Comment	30th September 2021
Target Publication Date (subject to change)	BP 2023
Notes	Revised monograph If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required. **Characteristics** Melting point requirement removed. **Related Substances** Correction factors for impurities A and F added. Column, mobile phase and system suitability updated. **Assay** Weight reduced from 500 mg to 300 mg.



$C_{18}H_{22}Cl_2N_2O_2$ 369.29 *78213-16-8*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Preparation

Diclofenac Gel

DEFINITION

Diclofenac Diethylamine is diethylammonium 2-[(2,6-dichloroanilino)phenyl]acetate. It contains not less than 99.0% and not more than 101.0% of $C_{18}H_{22}Cl_2N_2O_2$, calculated with reference to the dried substance.

CHARACTERISTICS

A white to light beige, crystalline powder.

Sparingly soluble in *water* and in *acetone*; freely soluble in *ethanol (96%)* and in *methanol*; practically insoluble in 1M *sodium hydroxide*.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of diclofenac diethylamine *(RS 371)*.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *methanol*.

(1) 5.0% w/v of the substance being examined.

(2) 5.0% w/v of *diclofenac diethylamine BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel precoated plate (Macherey Nagel SIL G-25 HR or silica gel $60F_{254}$ HPTLC plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a stream of warm air for 10 minutes. Spray with *ninhydrin solution* and heat at 110° for 15 minutes.

MOBILE PHASE

1 volume of *hydrochloric acid*, 1 volume of *water*, 6 volumes of *glacial acetic acid* and 11 volumes of *ethyl acetate*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (2) shows two clearly separated spots.

CONFIRMATION

The two principal spots in the chromatogram obtained with solution (1) are similar in position, colour and size to the corresponding spots in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH of a 1% w/v solution in *ethanol (10%)*, 6.4 to 8.4, Appendix V L.

Clarity and colour of solution

A 5% w/v solution in *methanol* is *clear*, Appendix IV A. The *absorbance* of the solution measured at 440 nm is not greater than 0.05, Appendix II B.

Related substances

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

(1) 0.10% w/v of the substance being examined.

(2) Dilute 2 volumes of solution (1) to 100 volumes and dilute 1 volume of this solution to 10 volumes.

(3) Dissolve 1 mg of *diclofenac for system suitability CRS* (containing impurities A and F) in 1 mL of the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (YMC-Pack Pro C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 1.5 times the retention time of diclofenac.

MOBILE PHASE

34 volumes of a mixture of equal volumes of a 0.05% w/v solution of *orthophosphoric acid* and a 0.08% w/v solution of *sodium dihydrogen orthophosphate*, previously adjusted to pH 2.5 with *orthophosphoric acid*, and 66 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to diclofenac (retention time about 25 minutes) are: impurity A, about 0.4 and impurity F, about 0.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to diclofenac impurity F and diclofenac is at least 4.0.

LIMITS

Identify any peak due to impurity A using the chromatogram obtained with solution (3) and multiply the area of the peak by a correction factor of 0.7. Identify any peak due to impurity F using the relative retention time and multiply the area of the peak by a correction factor of 0.3.

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Loss on drying

When dried at a pressure not exceeding 1 kPa for 24 hours, loses not more than 0.5% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A, Method II. Use 1 g.

ASSAY

Dissolve 0.3 g in 18 mL of *anhydrous acetic acid*. Carry out Method I for *non-aqueous titration*, Appendix VIII A, with *0.1M perchloric acid VS*, determining the end point potentiometrically. Each mL of *0.1M perchloric acid VS* is equivalent to 36.93 mg of $C_{18}H_{22}Cl_2N_2O_2$.

STORAGE

Diclofenac Diethylamine should be kept in an airtight container and protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Diclofenac Sodium.