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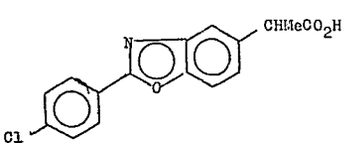
(54) **A novel crystalline form of benoxaprofen, methods of preparation thereof and pharmaceutical formulations containing said novel form.**

(57) A novel crystalline form of benoxaprofen, methods of preparation thereof and pharmaceutical formulations containing said novel form.

A thermodynamically stable polymorph of benoxaprofen, an antiinflammatory agent of the structural formula:



This stable polymorphic form, which can be prepared from the mastastable form by thermal treatment or crystallisation from a solution, is used in pharmaceutical formulations.

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A NOVEL CRYSTALLINE [illegible]

THEREOF AND PHARMACEUTICAL [illegible]

[illegible] TION

TO NOVEL FORM

This invention relates [illegible] form of a pharmacologically active substance [illegible] formulations containing the novel polymorph.

The compound [illegible]-4-phenyl-5-[illegible]oxazolylacetic acid, hereinafter referred to by the generic name benoxaprofen, is described in United Kingdom Patent Specification No. [illegible] and in an article in the Journal of Medicinal Chemistry, 13, 75 (1970) as a potent antiinflammatory agent. It is presently undergoing clinical trial.

Both the patent and the article are silent as regards polymorphic [illegible]. The laboratory procedures described in those publications [illegible] formation of the kinetically preferred polymorphic form, hereinafter referred to as "Form I", of benoxaprofen. However, this kinetically favoured polymorph is not the thermodynamically stable [illegible] form as hereinafter referred to as "Form II", and therefore tends to undergo polymorphic transformation on storage. For instance, [illegible] evening experiments carried out at temperatures between 4 and 37°C have shown 20% transformation of Form I to Form II after two years. When one considers that pharmaceutical formulations containing drugs of this type would generally be expected to have a shelf [illegible] of at least five years, it can be readily appreciated that the [illegible] nature of Form I presents various problems with respect to [illegible] viable compositions such as tablets, creams and suspensions. For a discussion [illegible] of [illegible] metastable forms [illegible] pharmaceutical formulations, reference may be made to the review article in Journal of Pharmacy [illegible] 58, 8, 911 (1969).

It is an object of the present invention to [illegible] form of benoxaprofen [illegible] the production [illegible].

[illegible] of the present invention there is provided a polymorphic form [illegible]

powder diffraction pattern using filtered copper-nickel radiation at $\lambda = 1.5405$.

"d" in Å	I/I_o
11.77	10
8.06	10
7.07	70
5.67	100
5.30	10
5.06	20
4.79	10
4.41	50
4.17	80
3.93	05
3.65	30
3.56	90
3.24	60
3.09	40
3.03	15
2.97	15
2.81	05
2.75	05
2.66	05
2.57	05
2.37	10
2.29	05
2.15	05
2.04	15
1.98	20
1.91	05
1.78	02

Form II, characterised as above, can also be distinguished from Form I by its infra red spectrum. Using a Perkin Elmer 297 spectrophotometer with benoxaprofen homogeneously dispersed in a potassium bromide disc, the following differences can be observed :-

1. Form I exhibits a sharp, medium intensity band at 880cm^{-1} whereas Form II exhibits a similar band at 885cm-1

2. In the region 1200 - 1330cm^{-1} both forms show a similar positioning of bands, but the intensities differ. In Form I the bands at 1220 and 1250cm^{-1} are considerably more intense than the others, whilst in Form II all bands are of similar intensity.

3. The strong band near 1700cm^{-1} is considerably sharper for Form I than for Form II.

Infra red analysis, which will be the usual method of assay of commercial material, is sensitive enough to detect as little as 10% by weight of Form I in batches of Form II material. Batches of Form II assayed by this spectral mode of analysis have proved to be quite satisfactory in pharmaceutical formulations such as tablets, capsules or suspensions, such formulations not deteriorating on storage.

According, in a second aspect of the invention there is provided Form II contaminated with less than 10% by weight of Form I.

According to a further aspect of the invention there is provided a pharmaceutical formulation comprising as an active material Form II associated with a pharmaceutically-acceptable carrier therefor.

The Form II polymorph in the above formulation should be pure as determined by the infra red assay technique described previously, i.e. it should contain less than 10% by weight of Form I.

Form II can be prepared from Form I by heating the latter material at a temperature in the range of from 90 to 170°C. For example Form I can be converted to Form II by heating in a fluid bed dryer at a temperature of approximately 115°C for upwards of 3 hours. The higher the temperature used the faster will be the polymorphic transformation from Form I to Form II. Alternatively, Form II may be prepared by slow and controlled crystallisation from solutions of benoxaprofen in n-butyl acetate.

Form II crystals of benoxaprofen can also be obtained by thermal decomposition at temperatures in the range 90-160°C. of the

ammonium salt of benoxaprofen, according to the procedure described in United States Patent 4,098,437. According to one aspect of this procedure, benoxaprofen ammonium salt is isolated directly from the hydrolysis of 2-(p-chlorophenyl)-2-methyl-5-benzoxazolylacetonitrile as an insoluble precipitate. The precipitate is collected and dried at a temperature in the above range, during which drying period the ammonium salt decomposes to yield dry benoxaprofen Form II crystals. Drying is continued until the decomposition of the ammonium salt is substantially complete. The yield of Form II material is usually in the range 95-98 percent.

Alternatively, the ammonium salt can be suspended in a solvent boiling in the range 90-160°C. and the resulting suspension or slurry heated, preferably by reflux; i.e. at the boiling point of the solvent, until the ammonium salt is substantially completely decomposed to ammonia and the free purified alkanoic acid. If the purified acid thus produced is substantially insoluble in the solvent used to slurry the ammonium salt (n-octane for example), benoxaprofen Form II will be obtained as from heating the salt in the absence of a solvent. If benoxaprofen is soluble in the solvent used to slurry the ammonium salt, (n-butyl acetate for example), a recrystallized product will be obtained. With either type of solvent benoxaprofen can be separated from the solvent by decantation or filtration. If benoxaprofen is soluble in the solvent employed, the solution is ordinarily concentrated and/or chilled to increase crystallisation and further crystals are obtained from the mother liquor.

The following non-limitative Examples will serve to illustrate the nature and advantages of the invention.

EXAMPLE 1

The process described in Method D, page 55 from Journal of Medicinal Chemistry, 18 (1975) was repeated exactly. The recrystallisation procedure adopted was conventional, i.e. the solution of benoxaprofen in ethanol was formed by warming on a steam bath and cooling of the thus-formed solution was effected using an ice-bath.

Infra red analysis and X-ray powder diffraction both showed that exclusive formation of Form I had occurred.

EXAMPLE 2

41 kg of 2-(4-chlorophenyl)-α-methyl-5-benzoxazolylacetonitrile were hydrolyzed in 12N aqueous hydrochloric acid by being stirred at 80°C for about two hours. The reaction mixture was cooled to about 40°C and then poured slowly with vigorous stirring into cold water. The solid precipitate of 2-(4-chlorophenyl)-α-methyl-5-benzoxazolylacetic acid thus prepared was collected by filtration and the filter cake washed with water until the washings no longer gave an acidic reaction to litmus. The filter cake was dried at 70-80°C; yield = 40 kg (77 percent purity). The filter cake was then dissolved in 48.3 litres of dimethylformamide at 55°C and the resulting solution diluted with about 180 litres of acetone. The resulting solution was filtered, the filtrate collected and about 11 litres of 28 percent aqueous ammonium hydroxide added very slowly to the filtrate maintained at about 35°C over a period of about 1/2 hour. During the addition of the aqueous ammonium hydroxide, the ammonium salt of 2-(4-chlorophenyl)-α-methyl-5-benzoxazolylacetic acid slowly precipitated yielding a slurry. After the addition of the ammonium hydroxide had been completed, the pH of the slurry was checked and found to be about 9. The slurry was next chilled in an ice-water mixture to about 0°C and the precipitated ammonium salt separated by filtration. The filter cake was washed with cold acetone (0°C) and the washed filter cake dried at 125°C for 3 hours in a tray dryer. During this heating and drying period the ammonium salt decomposed yielding, initially, the free acid, 2-(4-chlorophenyl)-α-methyl-5-benzoxazolylacetic acid as Form I which then underwent thermal conversion to Form II. 29.65 kg of purified free acid were obtained assayed at about 95 percent purity. The presence of Form II was demonstrated using X-ray powder diffraction and infra red analysis. Using the same drying system, the following times and temperatures were found to give Form II (97% or higher purity) 6 hours at 95°C, 2.5 hours at 125°C, 1.5 hours at 140°C, 0.5 hours at 155°C.

EXAMPLE 3

Benoxaprofen (892 g) Form I was suspended in n-butyl acetate (9.8 litres) and the stirred suspension heated to the reflux temperature of the solvent to form a solution. The temperature of the solution was then slowly reduced (10°C every hour) until room temperature was

The crystals of benoxaprofen thus produced were filtered off, washed with ethanol (892 ml) and dried in vacuo at 80°C. Yield 760g.

The infra red spectrum and X-ray powder diffraction of the crystals showed that pure form II had been obtained.

EXAMPLE 4

Tablets containing Benoxaprofen Form II were prepared using the following ingredients :

	Weight (mg)
Form II	100
Starch	55.1
Polyvinylpyrrolidone	8.25
Magnesium Stearate	1.65

The Form II and the starch were admixed and granulated with the polyvinylpyrrolidone as a 20% solution in water. Additional water was then added to form a suitable granulation which was passed through a stainless steel mesh screen with 1 mm apertures. The resultant granules were dried on a tray in a steam oven at 50 to 60°C. The dried granules were then passed through a screen (0.5 mm apertures) mixed with the magnesium stearate and compressed into tablets.

Tablets thus prepared were stored at 4, 25 and 40°C for two years. No deterioration in the physical characteristics of the tablets or in their appearance was noted over this period of time.

EXAMPLE 5

Benoxaprofen Form I was packed into glass ampoules (5 ml) and then subjected to cyclic temperature changes over two years. The weekl cycling programme adopted was that specified below :

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
37°C	4°C	15°C	37°C	4°C	15°C	15°C

This test is designed to mimic actual storage conditions. After two years the benoxaprofen was analysed and it was found (by infra-red analysis) that no less than 20% by weight of Form I had undergone polymorphic transformation to Form II. This experiment clearly illustrates the metastable nature of Form I.

CLAIMS

1. Benoxaprofen Form II.

2. Benoxaprofen Form II contaminated with less than 10% by weight of Form I.

3. A pharmaceutical formulation which contains as an active ingredient Benoxaprofen Form II as claimed in Claim 1 or 2, associated with a pharmaceutically-acceptable carrier therefor.

4. A method of preparing a pharmaceutical formulation which comprises admixing Form II as claimed in Claim 1 or 2 with a pharmaceutically-acceptable carrier therefor.

5. A method of preparing Form II which comprises heating Form I at a temperature between 90 and 170°C.

6. A method of preparing Form II which comprises the slow and controlled crystallisation of benoxaprofen from a solution in n-butyl acetate

European Patent Office

EUROPEAN SEARCH REPORT

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EP 78 30 0

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
DX	JOURNAL OF MEDICINAL CHEMISTRY, 18 (1975), 53-58. * Pages 54-55 *	1-4
DX	NL - A - 73 07018 (LILLY IND.) * Page 18; pages 37-39 * & DE - A - 2 324 443 & GB - A - 1 435 721	1-4
X	DE - A - 2 450 053 (LILLY IND.) * Page 39 * & NL 74 13848	1-4,6

CLASSIFICATION OF THE APPLICATION (Int. Cl.²)

C 07 D 263/56
A 61 K 31/42

TECHNICAL FIELDS SEARCHED (Int.Cl.²)

C 07 D 263/56
A 61 K 31/42

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
		ATLARD