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(54) Titre : NOUVEAU PROCEDE DE FABRICATION DE MESYLATE DE DOXAZOSINE LORS D'UNE MODIFICATION CRISTALLINE DESIGNEE PAR LA FORME A

(54) Title: NOVEL METHOD FOR PRODUCING DOXAZOSIN MESYLATE IN A CRYSTALLINE MODIFICATION DESIGNATED AS FORM A

(57) Abrégé/Abstract:
The invention relates to a method for producing doxazosin mesylate in the modification A. The method is characterised in that doxazosin and methane sulphonic acid are dissolved in a mixture containing an aprotic, polar organic solvent and methanol. Any clouding in the resulting solution is optionally eliminated. The clear solution thus produced is optionally injected with doxazosin mesylate crystals of form A, heated and isolated after the resulting product has been cooled. Said product is then washed with an organic solvent and dried.

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(54) Title: NOVEL METHOD FOR PRODUCING DOXAZOSIN MESYLATE IN A CRYSTALLINE MODIFICATION DESIGNATED AS FORM A

(54) Bezeichnung: NEUES VERFAHREN ZUR HERSTELLUNG VON DOXAZOSIN–MESYLAT IN EINER ALS FORM A BEZEICHNETEN KRISTALLMODIFIKATION

(57) Abstract

The invention relates to a method for producing doxazosin mesylate in the modification A. The method is characterised in that doxazosin and methane sulphonic acid are dissolved in a mixture containing an aprotic, polar organic solvent and methanol. Any clouding in the resulting solution is optionally eliminated. The clear solution thus produced is optionally injected with doxazosin mesylate crystals of form A, heated and isolated after the resulting product has been cooled. Said product is then washed with an organic solvent and dried.

(57) Zusammenfassung

Es wird ein Verfahren zur Herstellung von Doxazosin–Mesylat in der Modifikation A beschrieben, welches darin besteht, dass man Doxazosin mit Methansulfonsäure in einem Gemisch aus einem aprotischen, polaren organischen Lösungsmittel und Methanol löst, die so erhaltene Lösung gegebenenfalls von einer Trübung befreit und die dabei anfallende, klare Lösung gegebenenfalls mit Doxazosin–Mesylat–Kristallen der Form A animpft, erhitzt, nach dem Abkühlen das entstandene Produkt isoliert und dieses mit einem organischen Lösungsmittel wäscht und trocknet.

NOVEL METHOD FOR PRODUCING DOXAZOSIN MESYLATE IN A CRYSTALLINE MODIFICATION DESIGNATED AS A FORM A

The present invention relates to a novel process for preparing doxazosin mesylate in a crystal modification referred to as form A.

Doxazosin (= 4-amino-2-[4-(1,4-benzodioxan-2-carbonyl)-piperazin-1-yl]-6,7-dimethoxyquinazoline) is a known substance (Merck-Index 12th edition 1996, No. 3489) which lowers blood pressure. The substance is mainly used in the form of the monomesylate. An initial report of polymorphic forms of doxazosin mesylate appeared in the Chinese Journal of Medicinal Chemistry 5(4), 266-270 (1995). 3 crystal modifications of doxazosin mesylate are described therein. The various modifications are referred to as modifications A, B and C in the reference mentioned. Modification A is obtained on recrystallization of doxazosin mesylate from ethanol, while modifications B and C result from the recrystallization of doxazosin mesylate from chloroform and water respectively. Although the said reference speaks only of doxazosin, according to the published data the material is doxazosin mesylate.

Of the three forms, only form A is suitable for use for pharmaceutical purposes. The method for preparing form A of doxazosin mesylate indicated in the Chinese Journal of Medicinal Chemistry takes place by a recrystallization of doxazosin mesylate from ethanol which is, however, not a method which can be used on the industrial scale for obtaining specifically this modification.

EP-A 849 266 describes a doxazosin mesylate crystal modification which is referred to as form III and is identical to form A of doxazosin mesylate.

EP-A 849 266 also describes a process for preparing form A of doxazosin mesylate starting from doxazosin. This entails converting doxazosin, preferably in an organic solvent such as ethyl acetate, by heating with acetic acid into doxazosin acetate. The hot solution is filtered, treated with methanesulfonic acid and stirred where appropriate hot until crystallization occurs. The precipitated solvent adduct is removed after cooling and heated moist in a lower alcohol such as methanol or ethanol, the resulting solution is cooled and the

crystals which have separated out (= form A of doxazosin mesylate) are removed.

A further process for preparing doxazosin mesylate in modification A is described in PCT Application PCT/EP/9808360 of 18.12.1998. The starting material in this process is likewise doxazosin. To obtain form A of doxazosin mesylate, in this case doxazosin is dissolved with methanesulfonic acid in a mixture of an aprotic, polar organic solvent, for example N,N-dimethylformamide and N-methyl-2-pyrrolidone, and methanol, the solution obtained in this way is freed of turbidity where appropriate, and the resulting clear solution is stirred until no further precipitation occurs. The precipitate is removed (modification D of doxazosin mesylate), washed with methanol and heated in the moist state in ethanol. After cooling, the resulting modification A of doxazosin mesylate is isolated. The process also succeeds if only methanol is used to dissolve doxazosin with the methanesulfonic acid.

The reprecipitation of doxazosin mesylate from ethanol, which is indicated in the Chinese reference cited above for obtaining form A of doxazosin mesylate, is not, as already mentioned, a method which can be used on the industrial scale for obtaining doxazosin mesylate specifically in form A. In addition, this reference does not indicate the preparation of doxazosin mesylate which is used as starting material for preparing the individual forms either.

The two other methods indicated above for preparing form A of doxazosin mesylate could probably be used on a larger scale. However, both processes are very elaborate. In both cases, form A is not prepared simply by treating doxazosin with methanesulfonic acid. On the contrary, the method from EP 849 266 requires firstly preparation from doxazosin and acetic acid of the acetate, which is treated in solution with methanesulfonic acid. During this process, a solvent adduct crystallizes out and has to be isolated. Only on heating this adduct in a lower alcohol is the required form A of doxazosin mesylate then obtained. According to PCT/EP 9808360 there is firstly preparation from doxazosin and methanesulfonic acid of a form of doxazosin mesylate which is referred to as modification D and which has to be isolated. Only on subsequent heating of this form D in ethanol is the required form A of doxazosin mesylate obtained.

A simple process which can be used on the industrial scale for preparing doxazosin mesylate of modification A has now been found.

The invention relates to a process for preparing doxazosin mesylate in modification A, which comprises dissolving doxazosin with methanesulfonic acid in a mixture of an aprotic polar organic solvent and methanol, and where appropriate filtering the solution obtained thereby, where appropriate seeding with doxazosin mesylate crystals of form A, heating and, after cooling, isolating the resulting product and washing it with an organic solvent and drying it.

To react doxazosin with methanesulfonic acid, the two substances are employed in the molar ratio of about 1:1. A small molar excess (up to about 10%) of the sulfonic acid is preferably used.

Suitable aprotic polar organic solvents are N,N-dimethylformamide and, in particular, N-methyl-2-pyrrolidone. The ratio of doxazosin to methanol to aprotic polar organic solvent (weight/volume/volume) is about 1:((5 to 15):(1.5 to 4), preferably about 1: (8 to 12):(2 to 3). If the solution obtained by adding methanesulfonic acid to the mixture of doxazosin, methanol and aprotic polar organic solvent is turbid, it is advisable to remove the turbidity by, for example, filtration. If turbidity is to be removed, for example by filtration, it is expedient to add part of the methanol only after the filtration.

The clear solution obtained after adding methanesulfonic acid to the mixture of doxazosin, methanol and aprotic polar organic solvent, where appropriate after filtration, is subsequently heated, preferably after seeding with crystals of doxazosin mesylate of form A. This heating is preferably to a reflux temperature. The reaction mixture is heated at this temperature as a rule for 3 to 9 hours, preferably 4 to 6 hours.

The resulting suspension of crystals is then cooled to room temperature and subsequently stirred at room temperature for a short time. The solid product (modification A of doxazosin mesylate) is then isolated, washed with an organic solvent, preferably a lower alkyl alcohol, particularly preferably methanol, and dried in a conventional way, e.g. in vacuo.

The novel process provides doxazosin mesylate of modification A in a very simple manner and in an overall yield of more than 85%. The purity of the modification A obtained by the novel process is excellent. A considerable advantage of the novel process is also that a solution is produced after the addition of the methanesulfonic acid. This makes it possible to remove, by filtration, any foreign particles present.

Example 1

5.05 g of anhydrous methanesulfonic acid were added with stirring to a mixture of 22.6 g of doxazosin, 45 ml of N-methyl-2-pyrrolidone and 210 ml of methanol in a 500 ml three-neck round-bottom flask. During this, the internal temperature rose to 30°C, and a solution resulted. The reaction mixture was seeded with 0.5 g of doxazosin mesylate of form A, these seed crystals not dissolving. Seeding was followed by heating to the reflux temperature (boiling point 68°C; no solution) and stirring at this temperature for 4 h, during which further crystals formed. This was followed by cooling to room temperature and stirring at this temperature for 15 min. The precipitated product was filtered off by suction, washed 2x with 50 ml of methanol each time and dried at 75°C in vacuo. 24.6 g of doxazosin mesylate in form A were obtained. This corresponds to a yield of 87.8% based on doxazosin employed and subtracting the material used for seeding.

The doxazosin mesylate obtained in this way was used to determine the data shown in Figs. 1-3 for the Debye-Scherrer X-ray diffractogram, the differential scanning thermogram and the IR spectrum.

Example 2

5.05 g of anhydrous methanesulfonic acid were added with stirring to a mixture of 22.6 g of doxazosin, 45 ml of N-methyl-2-pyrrolidone and 210 ml of methanol, in a 500 ml three-neck round-bottom flask. During this, the internal temperature rose to 30°C, and a solution resulted. After the addition of methanesulfonic acid was complete, the mixture was heated to the reflux temperature (boiling point 68°C) and stirred at this temperature for 4 h (crystal formation during the stirring at the reflux temperature). This was followed by cooling to room temperature and stirring at this temperature for 15 min. The precipitated product was filtered off with suction, washed 2x with 50 ml of methanol each time and dried at 75°C in vacuo. 23.5 g of doxazosin mesylate of form A were obtained. This corresponds to a yield of 85.7% based on doxazosin employed.

Example 3

5.05 g of anhydrous methanesulfonic acid were added with stirring to a mixture of 22.6 g of doxazosin, 45 ml of N-methyl-2-pyrrolidone and 190 ml of methanol, in a 500 ml three-neck round-bottom flask. During this, the internal

temperature rose to 30°C, and a solution resulted. After the addition of methanesulfonic acid was complete, the reaction mixture was filtered into a second 500 ml three-neck round-bottom flask. The filter was then washed with 20 ml of methanol. The combined filtrates were heated to the reflux temperature (boiling point 68°C) and stirred at this temperature for 4 h (crystal formation during the stirring at the reflux temperature). After completion of the stirring time at the reflux temperature, the mixture was cooled to room temperature and stirred at this temperature for 15 min. The precipitated product was filtered off with suction, washed 2x with 50 ml of methanol each time and dried at 75°C in vacuo. 23.4 g of doxazosin mesylate in form A were obtained. This corresponds to a yield of 85.4% based on doxazosin employed.

We claim:

A process for preparing doxazosin mesylate in modification A, which comprises dissolving doxazosin with methanesulfonic acid in a mixture of an aprotic polar organic solvent and methanol, where appropriate filtering the solution obtained thereby, where appropriate seeding with doxazosin mesylate crystals of form A, heating and, after cooling, isolating the resulting product and washing it with an organic solvent and drying it.

FIG.

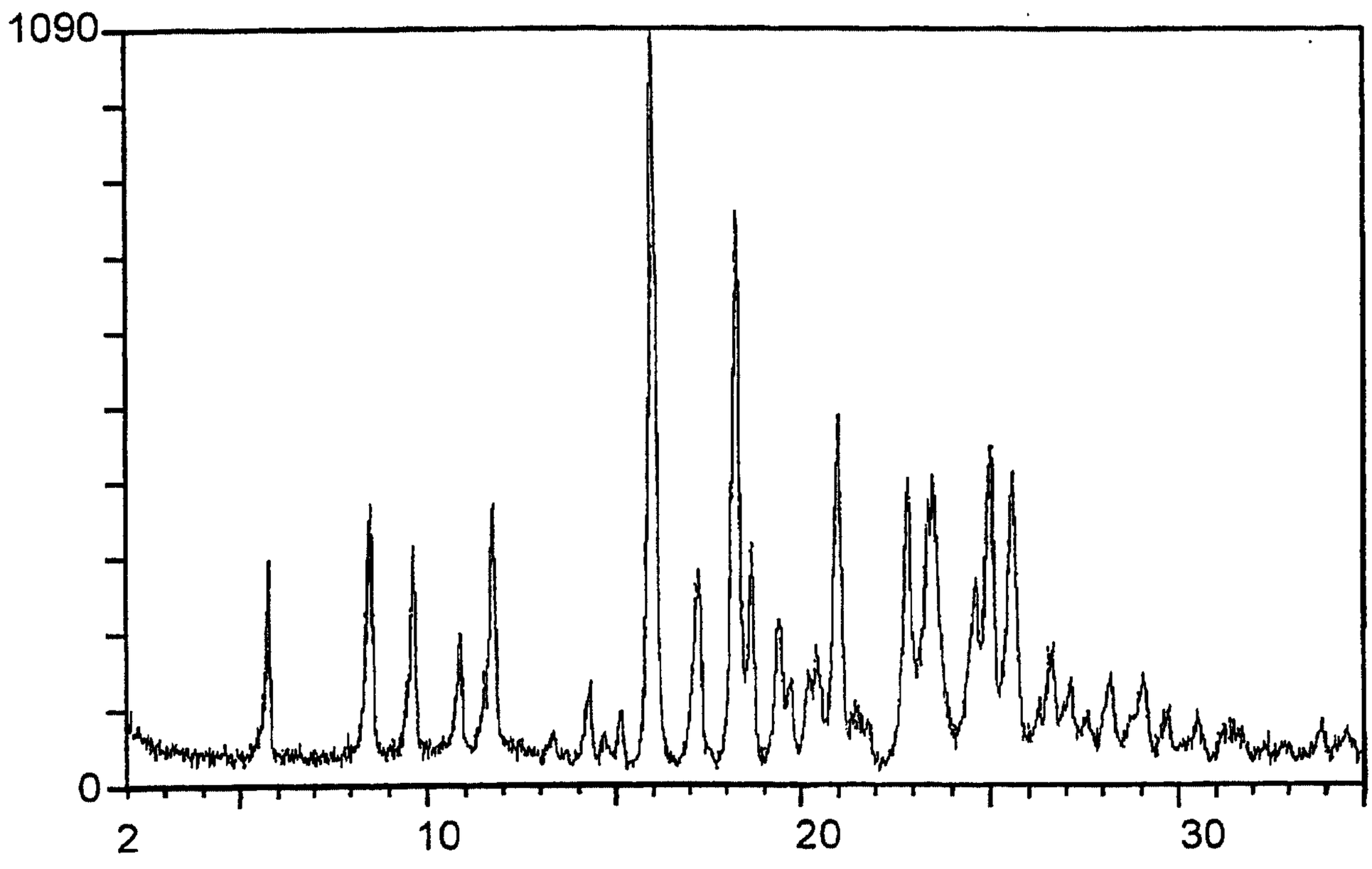
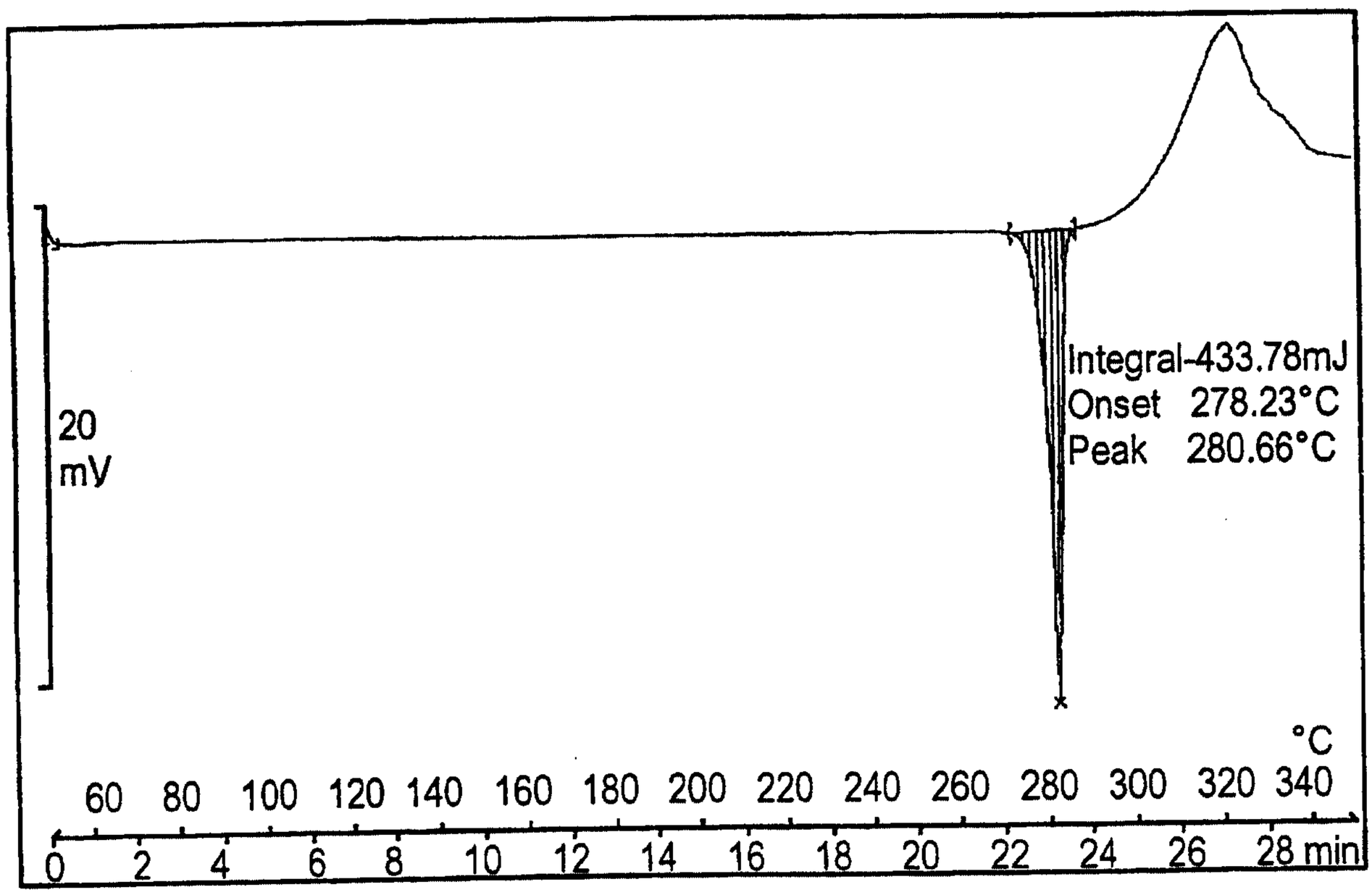


FIG.2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°C
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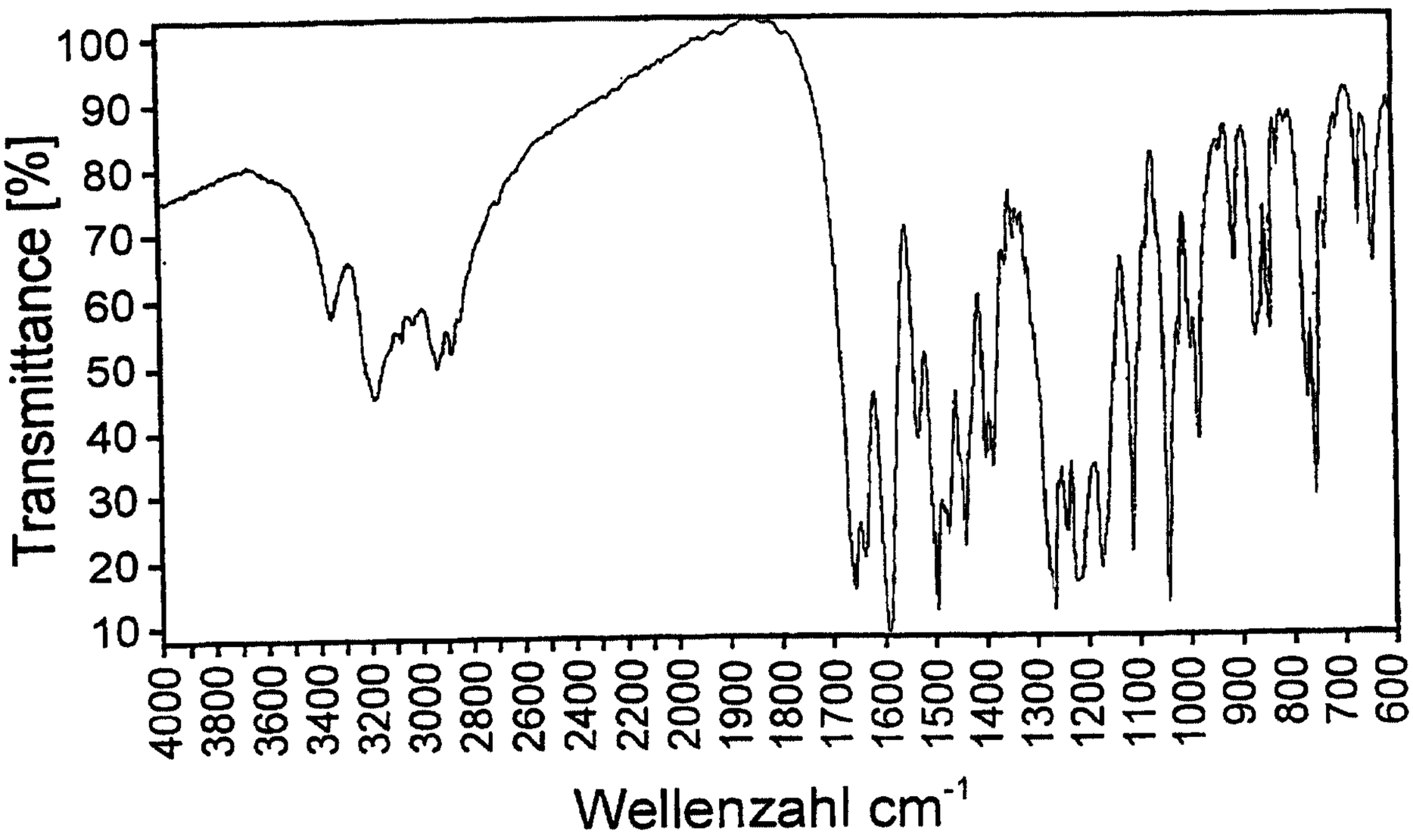
FIG.3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