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An agency of Industry Canada

CA 2165830 C 2005/04/26

(11)(21) 2 165 830

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 1994/06/30
(87) Date publication PCT/PCT Publication Date: 1995/01/12
(45) Date de délivrance/Issue Date: 2005/04/26
(85) Entrée phase nationale/National Entry: 1995/12/20
(86) N° demande PCT/PCT Application No.: GB 1994/001425
(87) N° publication PCT/PCT Publication No.: 1995/001324
(30) Priorité/Priority: 1993/07/01 (9313650.5) GB

(51) Cl.Int.^{6}/Int.Cl.^{6} C07C 217/10, A61K 31/135

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(54) Titre : SALMETEROL XINAFOATE A GRANULOMETRIE CONTROLEE
(54) Title: SALMETEROL XINAFOATE WITH CONTROLLED PARTICLE SIZE

(57) Abrégé/Abstract:
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2165830

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07C 215/60

A1

(11) International Publication Number: WO 95/01324

(43) International Publication Date: 12 January 1995 (12.01.95)

(21) International Application Number: PCT/GB94/01425

(22) International Filing Date: 30 June 1994 (30.06.94)

(30) Priority Data:
9313650.5 1 July 1993 (01.07.93) GB

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(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KE, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

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(57) Abstract

The invention relates to particulate products which may be prepared by methods and apparatus using supercritical fluids. More particularly the invention relates to pharmaceutical products, in particular easily handled and easily fluidised crystalline forms of salmeterol xinafoate, with controlled particle size and shape.

SALMETEROL XINAFOATE WITH CONTROLLED PARTICLE SIZE

The present invention relates to particulate products which may be prepared by methods and apparatus using supercritical fluids. More particularly, the invention relates to novel crystalline forms of salmeterol xinafoate.

The use of supercritical fluids (SCFs) and the properties thereof has been extensively documented, see for instance, J. W. Tom and P.G. Debendetti, "Particle Formation with Supercritical Fluids - A Review", *J. Aerosol. Sci.*, 22 (5), 555-584 (1991). Briefly, a supercritical fluid can be defined as a fluid at or above its critical pressure (Pc) and critical temperature (Tc) simultaneously. Supercritical fluids have been of considerable interest, not least because of their unique properties. These characteristics include:

- High diffusivity, low viscosity and low surface tension compared with liquids.

- Large compressibility of supercritical fluids compared with the ideal gas implies large changes in fluid density for slight changes in pressure, which in turn results in highly controllable solvation power. Supercritical fluid densities typically range from 0.1-0.9 g/ml under normal working conditions. Thus, selective extraction with one supercritical fluid is possible.

- Many supercritical fluids are normally gases under ambient conditions, which eliminates the evaporation/concentration step needed in conventional liquid extraction.

- Most of the commonly used supercritical fluids create non-oxidising or non-degrading atmospheres for sensitive and thermolabile compounds, due to their inertness and moderate temperatures used in routine working conditions. Carbon dioxide is the most extensively used SCF due to its cheapness, non-toxicity, non-flammability and low critical temperature.

These characteristics have led to the development of several techniques of extraction and particle formation utilising supercritical fluids. In particular, two processing methods have been identified for particle formation.

Rapid Expansion of Supercritical Solution (RESS) (see, for instance, J.W. Tom and P.G. Debendetti, *supra*) involves the dissolution of the solute of interest in the supercritical fluid, followed by rapid expansion of the supercritical solution to atmospheric pressure, resulting in the precipitation of particles.

Gas Anti Solvent (GAS) Recrystallisation (P.M. Gallagher et al, Supercritical Fluid Science and Technology, *ACS Symp. Ser.*, 406, p.334 (1989)) is particularly useful in situations when the solid of interest does not dissolve, or has a very low solubility in a supercritical fluid or a modified supercritical fluid. In this technique, the solute of interest is dissolved in a conventional solvent. A supercritical fluid such as carbon dioxide is introduced into the solution, leading to a rapid expansion of its volume. As a result, the solvent power decreases dramatically over a short period of time, triggering the precipitation of particles.

Both of these techniques, when applied to particle formation, have their limitations. Thus, when using RESS, the product yield is usually low due to the low solubility of many polar solutes (e.g. many pharmaceutical products) in supercritical carbon dioxide under normal working conditions. This, together with difficulties in collecting the products makes the technique time consuming and unattractive as a method of routine particle formation. In practice, the combination of high energy requirements of RESS and low yield has greatly limited the application of this technique.

Regarding GAS, the selection of solutes, solvents and the supercritical fluid requires careful consideration. The solubility of the solute in the sub/supercritical fluid should be low whilst, at the same time, the sub/supercritical fluid should expand the solvent appreciably. These operating criteria, in addition to experimental difficulties and high energy costs, have limited the use of this technique, as have problems with product recovery and solvent recovery/recycling every time the system is depressurised, see for instance P.M. Gallagher et. al., *J Supercritical Fluids*, 5, 130-142 (1992).

The limitations of the RESS and GAS techniques are such that it is generally considered that these approaches to routine particle formation should only be used when all conventional methods prove inadequate.

The concept of spraying liquid mixtures in supercritical fluids such as carbon dioxide, or vice versa, has been employed in extraction procedures involving solvents for a decade (see for instance R. J. Lahiere & J. R. Fair in *Ind. Eng. Chem. Res.*, 26, 2086-2092 (1987)).

More recently, US Patent Number 5,043,280 describes a method for the manufacture of a preparation comprising a substance or substances, such as a medically useful substance, and a carrier or carriers, such as a pharmaceutically acceptable carrier, which avoids or lacks a solvent residue, or at least reduces the solvent residue to a toxicologically harmless amount. The method essentially involves the use of a fluid, at a supercritical state when introduced into a spray tower, to extract a solvent from sprayed solution(s) of a substance and a carrier, to form a sterile product containing a substance embedded in a carrier. It should be noted, however, that the method has no means for controlling the physical properties of the particulate products which are formed by the method.

In many fields, and especially in the fields of pharmaceuticals, photographic materials, explosives and dyes, there is a need for techniques whereby a product may be obtained with consistent and controlled physical criteria, including control of particle size and shape, quality of the crystalline phase, chemical purity and enhanced handling and fluidising properties.

In addition, it would be advantageous to prepare micron-sized particles directly without the need to mill products to this size range. Such milling leads to associated problems such as increased static charge and enhanced particle cohesiveness, as well as reduced yield of product.

Described herein is an apparatus for the formation of a particulate product in a controlled manner utilising a supercritical fluid particle formation system. The apparatus comprises a particle formation vessel with means for controlling the temperature of said vessel and means for controlling the pressure of said vessel, together with a means for the co-introduction into said vessel of a supercritical fluid and a vehicle containing at least one substance in solution or suspension, into said vessel, such that dispersion and extraction of the vehicle occur substantially simultaneously by the action of the supercritical fluid.

As used herein, the term "supercritical fluid" means a fluid at or above its critical pressure (Pc) and critical temperature (Tc) simultaneously. In practice, the pressure of the fluid is likely to be in the range 1.01 Pc - 7.0 Pc, and its temperature in the range 1.01 Tc - 4.0 Tc.

The term "vehicle" means a fluid which dissolves a solid or solids, to form a solution, or which forms a suspension of a solid or solids which do not dissolve or have a low solubility in the fluid. The vehicle can be composed of one or more fluids.

As used herein, the term "supercritical solution" means a supercritical fluid which has extracted and dissolved the vehicle.

The term "dispersion" means the formation of droplets of the vehicle containing at least one substance in solution or suspension.

The term "particulate product" includes products in a single-component or multi-component (e.g. intimate mixtures of one component in a matrix of another) form.

It will be appreciated that, where necessary, the apparatus may additionally comprise a means for the collection of the particulate product, for example, a means for the retention of the product in the particle formation vessel, such as a filter, thus reducing loss of the product together with the resultant supercritical solution. An alternative means may involve a cyclone separating device.

In one embodiment, the apparatus may include means for recovering the supercritical solution formed on extraction of the vehicle into the supercritical fluid; means for separating the components of the supercritical solution; and optionally means for recycling one or more of said components back into the apparatus, so as to increase its overall efficiency.

It will be further appreciated that the apparatus may comprise more than one particle formation vessel and/or means for the collection of the particulate product, thereby allowing for the substantially continuous operation of the apparatus through simple switching from one particle formation vessel or collection vessel to another as required.

The apparatus described above and its use provide the opportunity for manufacturing dry particulate products with controlled particle size and shape by offering control over the working conditions, especially the pressure, utilising, for example, an automated back-pressure regulator such as model number 880-81 produced by Jasco Inc. Such an improved control eliminates pressure fluctuation across the particle formation vessel and ensures a more uniform dispersion of the vehicle (containing at least one substance in solution or suspension) by the supercritical fluid with narrow droplet size distribution during the particle formation process. There is little or no chance that the dispersed droplets will reunite to form larger droplets since the dispersion occurs by the action of the supercritical fluid which also ensures thorough mixing with the vehicle and rapidly removes the vehicle from the substance(s) of interest, leading to particle formation.

The simultaneous co-introduction of the vehicle containing at least one substance in solution or suspension and the supercritical fluid, according to the method described herein, allows a high degree of control of parameters such as temperature, pressure and flow rate, of both vehicle fluid and supercritical fluid, at the exact point when they come into contact with one another.

Further advantages for particles formed as described herein include control over the quality of the crystalline and polymorphic phases, since the particles will experience the same stable conditions of temperature and pressure when formed, as well as the potential of enhanced purity. This latter feature can be attributed to the high selectivity of supercritical fluids under different working conditions, enabling the extraction of one or more of the impurities from the vehicle containing the substance of interest.

Moreover, the co-introduction of the vehicle and supercritical fluid, leading to simultaneous dispersion and particle formation, allows particle formation to be carried out, if desired, at temperatures at or above the boiling point of the vehicle, something not possible using known supercritical fluid particle formation techniques. This enables operation in temperature and pressure domains which were previously inaccessible, which in turn can allow the formation of products, or particular forms of products, that previously could not have been achieved. This, together with the high degree of control of the operating conditions made possible by the apparatus and method described herein, means that its uses could be extremely wide-ranging and its versatility of value in many fields.

A further advantage of the apparatus described herein is that it can allow particle formation to occur in a completely closed environment, i.e. in a closed particle formation vessel. The apparatus can be sealed from the atmosphere, making it easy to maintain sterile operating conditions and also reducing the risk of environmental pollution and it can also be kept free of oxygen, moisture or other relevant contaminants. The particle formation vessel can also easily be made light-free, of particular use for the preparation of photosensitive products such as for use in the photographic industry.

The means for the co-introduction of the supercritical fluid and the vehicle into the particle formation vessel preferably allows for them to be introduced with concurrent directions of flow, and more preferably takes the form of a coaxial nozzle as described below. This ensures no contact between the formed particles and the vehicle fluid around the nozzle tip area. Such contact would reduce control of the final product size and shape. Extra control over the droplet size, in addition to that provided by nozzle design, is achieved by controlling the flow rates of the supercritical fluid and the vehicle fluid. At the same time, retaining the particles in the particles formation vessel eliminates the potential of contact with the vehicle fluid that might otherwise take place on depressurising the supercritical solution. Such contact would affect the shape and size, and potentially the yield, of the product.

Thus, in the apparatus described herein, the means for the co-introduction of the supercritical fluid and the vehicle (containing at least one substance in solution or suspension) into the particle formation vessel preferably comprises a nozzle the outlet end of which communicates with the interior of the vessel, the nozzle having coaxial passages which terminate adjacent to one another at the outlet end, at least one of the passages serving to carry a flow of the supercritical fluid, and at least one of the passages serving to carry a flow of the vehicle in which a substance is dissolved or suspended.

Preferably, the opening at the outlet end (tip) of the nozzle will have a diameter in the range of 0.05 to 2mm, more preferably between 0.1 and 0.3mm, typically about 0.2mm. The angle of taper of the outlet end will depend on the desired velocity of the fluids introduced through the nozzle; an increase in the angle may be used, for instance, to increase the velocity of the supercritical fluid introduced through the nozzle and hence to increase the amount of physical

contact between the supercritical fluid and the vehicle. Typically (although not necessarily) the angle of taper will be in the range of about 10° to about 50°, preferably between about 20° and about 40°, more preferably about 30°. The nozzle may be made of any appropriate material, for example stainless steel.

In one embodiment, the nozzle has two coaxial passages, an inner and an outer. In another, preferred, embodiment, the nozzle has three coaxial passages, an inner, an intermediate and an outer. This latter design allows greater versatility in use of the apparatus, since if necessary two vehicles may be introduced into the particle formation vessel with the supercritical fluid. Improved dispersion and finer particles can also be obtained if such a nozzle is used to introduce a flow of the vehicle sandwiched between an inner and an outer flow of the supercritical fluid, since this ensures that both sides of the vehicle are exposed to the supercritical fluid. It is, however, to be appreciated that the nozzle may have any appropriate number of coaxial passages.

The internal diameters of the coaxial passages may be chosen as appropriate for any particular use of the apparatus. Typically, the ratio of the internal diameters of the outer and the inner passages may be in the range of from 2 to 5, preferably between about 3 and 5. Where an intermediate passage is included, the ratio of the internal diameters of the outer and intermediate passages may be in the range of from 1 to 3, preferably between about 1.4 and 1.8.

Particular examples of such coaxial nozzles and their typical dimensions are illustrated in Figures 2A, 2B and 25.

The temperature of the particle formation vessel may be maintained (preferably ± 0.1°C) by means of a heating jacket or, more preferably, an oven. The pressure of the particle formation vessel is conveniently maintained (preferably ± 2 bar) by means of a back-pressure regulator. It will be appreciated that such apparatus will be readily available from, for example, manufacturers of supercritical fluid extraction equipment, for instance, from Jasco Inc., Japan.

In a further aspect, there is provided a method for the formation of a particulate product which comprises the co-introduction of a supercritical fluid and a vehicle containing at least one substance in solution or suspension into a particle formation vessel, the temperature and pressure in which are controlled, such

that dispersion and extraction of the vehicle occur substantially simultaneously by the action of the supercritical fluid. Dispersion and extraction will also typically occur substantially immediately on introduction of the fluids into the particle formation vessel. Co-introduction of the supercritical fluid and the vehicle containing a substance in solution or suspension preferably is effected using a nozzle of coaxial design.

Suitable chemicals for use as supercritical fluids include carbon dioxide, nitrous oxide, sulphur hexafluoride, xenon, ethylene, chlorotrifluoromethane, ethane and trifluoromethane. Particularly preferred is carbon dioxide.

The supercritical fluid may optionally contain one or more modifiers, for example, but not limited to, methanol, ethanol, isopropanol or acetone. When used, the modifier preferably constitutes not more than 20%, and more particularly constitutes between 1 and 10%, of the supercritical fluid.

The term "modifier" is well known to those persons skilled in the art. A modifier (or co-solvent) may be described as a chemical which, when added to a supercritical fluid, changes the intrinsic properties of the supercritical fluid in or around the critical point.

It will be appreciated that the choice of vehicle for the substance(s) of which the product is to be formed will be dependent upon the particular substance(s). Thus, where the substance is to be handled as a solution the solid should be soluble in the chosen vehicle, and the chosen vehicle should be soluble in the chosen supercritical fluid. The choice of a suitable combination of supercritical fluid, modifier (where desired) and vehicle for any desired product will be well within the capabilities of a person of ordinary skill in the art.

In one particularly preferred embodiment of the present invention, the product to be formed is a pharmaceutical compound, in particular salmeterol xinafoate, in which case a suitable solvent may be, for example, methanol, ethanol, isopropanol, acetone or any mixture thereof.

Control of parameters such as size and shape in the particulate product will be dependent upon the operating conditions used when carrying out the method of the invention. Variables include the flow rates of the supercritical fluid and/or

the vehicle containing substance(s), the concentration of the substance(s) in the vehicle, and the temperature and pressure inside the particle formation vessel.

It will also be appreciated that the precise conditions of operation of the present apparatus will be dependent upon the choice of supercritical fluid and whether or not modifiers are present. Table 1 lists the critical pressure and temperatures for some selected fluids:

Table 1

Fluid	Pc (bar)	Tc (°C)
carbon dioxide	74	31
nitrous oxide	72	36
sulphur hexafluoride	37	45
xenon	58	16
ethylene	51	10
chlorotrifluoromethane	39	29
ethane	48	32
trifluoromethane	47	26

In practice, it may be preferable to maintain the pressure inside the particle formation vessel substantially in excess of the Pc (for instance, 100-300 bar for carbon dioxide) whilst the temperature is slightly above the Tc (e.g. 40-60°C for carbon dioxide).

The flow rates of the supercritical fluid and/or the vehicle may also be controlled so as to achieve a desired particle size, shape and/or form. Typically, the ratio of the vehicle flow rate to the supercritical fluid flow rate will be between 0.001 and 0.1, preferably between 0.01 and 0.07, more preferably around 0.03.

The method described herein preferably additionally involves collecting the particulate product following its formation. It may also involve recovering the supercritical solution formed, separating the components of the solution and recycling one or more of those components for future use.

According to a preferred aspect of the present invention, there is provided the compound 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-

benzenedimethanol (salmeterol), 1-hydroxy-2-naphthalenecarboxylate (xinafoate) in an easily handled and easily fluidised crystalline form, with a controlled particle size and shape.

Conventionally crystallised salmeterol xinafoate, even after micronisation (fluid milling), exists in a form with poor flow characteristics, for example it is cohesive and statically charged, which results in difficulties in handling the drug substance in pharmaceutical formulation processes.

In another aspect of the present invention, there is provided salmeterol xinafoate in a form with a dynamic bulk density of less than 0.1g.cm^{-3}. In a preferred aspect of the present invention, there is provided salmeterol xinafoate in a form with a dynamic bulk density in the range between 0.01 and 0.1g.cm^{-3}, and in particular, in the range between 0.01 and 0.075g.cm^{-3}.

The dynamic bulk density (W) is indicative of a substance's fluidisability and is defined as:

$$W = \frac{(P-A)C}{100} + A$$

where P is the packed bulk density (g.cm^{-3}), A is the aerated bulk density (g.cm^{-3}) and C is the compressibility (%) where C is calculated by the equation:

$$C = \frac{P-A}{P} \times 100$$

Clearly, a low figure for W corresponds to a high degree of fluidisability.

When compared against conventionally crystallised salmeterol xinafoate, both before and after micronisation, the salmeterol xinafoate of the present invention exhibits a significantly lower dynamic bulk density than the conventionally crystallised salmeterol xinafoate as illustrated in Table 2 (see Example 1 below).

It will be appreciated that in the case of an inhaled pharmaceutical, such as salmeterol xinafoate, it is particularly desirable to produce a drug substance

which is readily fluidisable, thereby potentially improving its inhalation properties.

The salmeterol xinafoate of the present invention is observed to have improved handling and fluidising characteristics compared with conventionally crystallised salmeterol xinafoate.

Furthermore, the particle size and shape of the salmeterol xinafoate of the present invention can be controlled as illustrated by the electron-micrographs herein.

Preferably, the salmeterol xinafoate of the present invention is within the particle size range suitable for pharmaceutical dosage forms to be delivered by inhalation or insufflation. A suitable particle size range for this use is 1 to 10 microns, preferably 1 to 5 microns. Particles generally have a uniform particle size distribution, as measured by a uniformity coefficient of from 1 to 100, typically 1 to 20 e.g. 5 to 20.

The particle size distribution of the salmeterol xinafoate according to the invention may be measured by conventional techniques, for example by laser diffraction or by the "Twin Impinger" analytical process. As used herein reference to the "Twin Impinger" assay means "Determination of the deposition of the emitted dose in pressurised inhalations using apparatus A" as defined in British Pharmacopoeia 1988, pages A202-207, Appendix XVII C as applied to a dry powder inhalation formulation. Such techniques enable the "respirable fraction" of the particulate substance to be calculated. As used herein reference to "respirable fraction" means the amount of active ingredient collected in the lower impingement chamber per actuation expressed as a percentage of the total amount of active ingredient delivered per actuation using the twin impinger method described above. The preferred salmeterol xinafoate according to the invention of mean particle size between 1 and 10 microns has been found to have a respirable fraction of 14% or more by weight, preferably 15 to 30%, for example 18 to 25%.

The salmeterol xinafoate of the present invention typically has a low cohesivity, for example of 0 to 20%, preferably 0 to 5% employing methods of measurement based on those described by R L Carr in Chemical Engineering 1965, 163-168.

It has also been found that conventionally crystallised salmeterol xinafoate, when studied by differential scanning calorimetry (DSC), shows a transition between two forms (hereinafter "Polymorph I" and "Polymorph II") occurring between 120 and 140°C. A DSC profile for conventionally crystallised salmeterol xinafoate showing the characteristic two peaks for Polymorphs I and II is shown in Figure 3.

There is also provided, in a further aspect of the present invention, salmeterol xinafoate in the form of pure Polymorph I, characterised by a single endotherm at about 123.5°C recorded by DSC - see Figure 4 and Example 2.

In another aspect of the present invention, there is provided salmeterol xinafoate in the form of pure Polymorph II, characterised by a single endotherm at about 135.8°C recorded by DSC - see Figure 6 and Example 2. Mixtures of the two polymorphs, in controlled proportions, were also achieved in Example 2.

The prepared polymorphs are also stable, meaning that there is no transition from one polymorph to another observed under the DSC conditions.

The salmeterol xinafoate according to the invention may be used to prepare a pharmaceutical composition which further comprises a pharmaceutically acceptable carrier. Preferred carriers include, for example polymers e.g. starch and hydroxypropylcellulose, silicon dioxide, sorbitol, mannitol and lactose e.g. lactose monohydrate. In a preferred pharmaceutical composition according to the invention the salmeterol xinafoate and carrier are co-crystallised together using the process and apparatus described herein to form multicomponent particles comprising both salmeterol xinafoate and carrier. Such multicomponent particles represent a further aspect of the invention.

In a preferred aspect the invention provides a pharmaceutical composition in the form of a dry powder suitable for inhalation which comprises salmeterol xinafoate according to the present invention and lactose as carrier. Especially preferred are compositions comprising salmeterol xinafoate and lactose in the form of multicomponent particles.

Accordingly, in a further aspect the present invention resides in 4-Hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3- benzenedimethanol (salmeterol), 1-hydroxy-2-naphthalenecarboxylate (xinafoate) in an easily handled and easily fluidised crystalline form, with a dynamic bulk density of less than 0.1 $g.cm^{-3}$.

There follows a brief description of the Figures:

Figure 1 shows a schematic design of an apparatus described herein.

Figure 2A shows a cross-section of a coaxial nozzle for use in the apparatus described herein.

Figure 2B shows a longitudinal section of the tip of a coaxial nozzle for use in the apparatus described herein.

Figure 3 is a differential scanning calorimetry (DSC) profile of conventionally crystallised salmeterol xinafoate.

Figure 4 is a DSC profile of Polymorph I of salmeterol xinafoate, as prepared in Example 2.

Figure 5 is an X-ray powder diffraction (XRD) pattern of Polymorph II of salmeterol xinafoate, as prepared in Example 2.

Figure 6 is a DSC profile of Polymorph II of salmeterol xinafoate, as prepared in Example 2.

Figure 7 is an expanded XRD pattern of Polymorph II of salmeterol xinafoate, as prepared in Example 2.

Figures 8 to 11 are DSC profiles and XRD patterns showing a mixed phase status of Polymorph I and II of salmeterol xinafoate, obtained by varying the operating conditions in Example 2.

Figures 12 to 16 are scanning electron microscopy (SEM) photographs of salmeterol xinafoate, as prepared in Example 3.

Figures 17 to 19 are SEM photographs of salmeterol xinafoate, as prepared in Example 4.

Figure 20 is a DSC profile of salmeterol xinafoate deposited onto silicon dioxide fumed particles, as prepared in Example 5.

Figure 21 is a DSC profile of salmeterol xinafoate, as prepared in Example 5 for comparison.

Figure 22 is an XRD pattern of salmeterol xinafoate deposited onto silicon dioxide fumed particles, as prepared in Example 5.

Figure 23 is an XRD pattern of salmeterol xinafoate, as prepared in Example 5 for comparison.

Figures 24A and 24B show schematic designs of alternative apparatuses.

Figure 25 shows a longitudinal section of the tip of an alternative coaxial nozzle.

Figure 26 is a longitudinal cross-section through a particle formation vessel.

Figures 27A-F show the components of the vessel of Figure 26.

Figures 28 and 29 are SEM photographs of salmeterol xinafoate, prepared according to Example 6.

Figure 30 is an XRD pattern for the salmeterol xinafoate prepared according to Example 6.

Figures 31-33 are graphs showing the effects of operating conditions on product particle size, when carrying out a method as described herein.

Figure 34 is an XRD pattern for salmeterol xinafoate prepared according to Example 8.

Figures 35 and 36 are XRD patterns for matrices of salmeterol xinafoate and hydroxypropylcellulose prepared according to Example 10.

Figures 37 and 38 are SEM photographs of salmeterol xinafoate produced by the method of Example 11.

Figures 39 and 40 are HPLC chromatograms for pure salmeterol xinafoate and pure salicylic acid respectively, as used in Example 12.

Figure 41 is a HPLC chromatogram for the sample of salmeterol xinafoate and salicylic acid used in Example 12.

Figure 42 is a HPLC chromatogram for the product prepared according to Example 12.

Figure 43 is an SEM micrograph of alpha-lactose monoydrate prepared according to Example 13, at 270 bar and 70°C.

Figure 44 is an XRD pattern for the sample shown in Figure 43.

Figure 45 is an SEM micrograph of alpha-lactose monohydrate prepared according to Example 13, at 150 bar and 50°C.

Figure 46 is an XRD pattern for the sample shown in Figure 45.

Figures 47 and 48 are XRD patterns for matrices of salmeterol xinafoate and hydroxypropylcellulose prepared according to Example 14.

There follows a detailed description of a preferred embodiment of the apparatus and method described herein with reference to Figures 1, 2, 24 and 25. Figures 1 and 24 are simplified diagrammatic flow sheets of apparatus, and Figures 2A, 2B and 25 show nozzles which may be used therein.

Referring to Figure 1, the apparatus includes a particle formation vessel **6**. This is typically a standard reaction vessel, for instance of the type available from Keystone Scientific Inc., of an appropriate capacity for the particular use to which it is to be put. The temperature and pressure of the vessel are maintained at constant desired level, by means of an oven **7** and back-pressure regulator **8**, respectively.

In use, the system is initially pressurised and stable working conditions are met. A suitable gas, for example, carbon dioxide, is fed from source **1** via conduit **11** to a cooler **2**, to ensure liquification, and is fed by conduit **12** to a pump **4**. From there it is fed by conduit **13** to the vessel **6** via a nozzle **20** . A solution or dispersion of a solid of interest, for example, salmeterol xinafoate, in a suitable vehicle, for example methanol, is drawn from source **5** by a conduit **14** to a pump **3** and is fed by conduit **15** to the vessel **6** via a nozzle **20**.

The nozzle **20** may be as shown in either Figure 2 (A and B) or Figure 25. That shown in Figure 2 comprises coaxial inner and outer tubes **30** and **40**,

respectively. These define an inner passage **31** and an outer passage **41**. The tubes **30** and **40** have conically tapering end portions **32** and **42**, respectively. The tips of the end portions **32** and **42** define respective orifices **33** and **43**, with the orifice **43** being a short distance downstream of the orifice **33**. As indicated in Figure 2B, the angle of taper of the end portion **42** is about 30° in this(non-limiting) example.

The alternative nozzle illustrated in Figure 25 comprises three coaxial tubes **50**, **60** and **70** which define an inner passage **51**, an intermediate passage **61**, and an outer passage **71** respectively. Tubes **60** and **70** have conically tapering end portions **62** and **72**, the angle of taper of the end portion **72** being about 30° in this example.

The nozzle of Figure 25 allows three fluids to be introduced into the vessel **6** at the same time, leading to greater versatility in use of the apparatus. For instance, it is possible to add through one of the three passages a desired carrier or other additive intended to form part of, or be mixed with, the final particulate product. The additive is then dispersed simultaneously with the substance of primary interest. Also, <u>in situ</u> reactions may be carried out immediately prior to dispersion by the supercritical fluid, by introducing two or more reactants in two separate vehicles through two of the nozzle passages, the reaction occurring at the passage outlets either immediately prior to, or on, dispersion.

Alternatively, the nozzle of Figure 25 may be used to introduce a flow of the vehicle (passage **61**) sandwiched between an inner and an outer flow of the supercritical fluid (passages **51** and **71**). This leads to improved dispersion of the vehicle, and hence to greater control over, and uniformity of, particle size in the final product; indeed it makes possible the formation of finer products than may be achieved using a two-passage nozzle.

In the nozzle shown, inner tube **50** has an internal diameter of 0.25mm; intermediate tube **60** has an internal diameter of 0.53mm; and outer tube **70** has an internal diameter of 0.8mm and an outside diameter of 1.5mm. The tip opening (**73**) has an internal diameter of 0.2mm. The tubes are all made of stainless steel.

However, the nozzle may be made of any appropriate material and have any suitable dimensions. For instance, the internal diameters may be in the ranges 0.05 -0.35mm (inner); 0.25 -0.65mm (intermediate); and 0.65 -0.95mm (outer), preferably between 0.1 and 0.3mm (inner); 0.3 and 0.6mm (intermediate); and 0.7 and 0.9mm (outer). The tip opening is likely to have an internal diameter in the range of 0.1 - 0.3mm, preferably between 0.18 and 0.25.

In the apparatus of Figure 1, the supercritical fluid is fed under pressure (at a high flow rate when compared with the flow rate of the vehicle) through for example the inner nozzle passage **31** of the nozzle shown in Figure 2, and the solution or suspension of the solid of interest in a vehicle (hereinafter referred to as the "liquid") is simultaneously fed under pressure through the outer passage **41**. It is believed that the high velocity supercritical fluid emerging from the orifice **33** causes the liquid emerging from the end of outer passage **41** to be broken up into droplets from which the vehicle is substantially simultaneously extracted by the supercritical fluid to result in the formation of particles of the solid previously held in the vehicle. It is to be understood, however, that although it is believed that this is what occurs, we do not wish to be bound by this theoretical explanation, and the actual physical processes occurring may not be precisely as just indicated.

Also, although the configuration has been described in which the supercritical fluid passes through the inner passage **31** and the vehicle passes through the outer passage **41**, the configuration may be reversed, with the supercritical fluid in the outer passage **41** and the vehicle in the inner passage **31**. Similarly in the nozzle of Figure 25, any one of the three passages may be used to carry any one of a number of desired fluids, as appropriate.

The nozzle **20** ensures dispersion of the vehicle containing the solid of interest by the shearing action of the high velocity supercritical fluid and also thorough mixing of the dispersed vehicle with the supercritical fluid which simultaneously extracts the vehicle from the dispersed liquid, resulting in substantially immediate particle formation of the solid of interest. Because the supercritical fluid and vehicle are introduced coaxially, and dispersion occurs substantially simultaneously with vehicle extraction, a very high degree of control is possible of the conditions (e.g. pressure, temperature and flow rate) affecting particle formation, at the exact time when it occurs.

The particles formed are retained in the particle formation vessel by collecting means **21**. The resultant supercritical solution is fed by conduit **16** to a back-pressure regulator **8** and is then fed by conduit **17** to a separation vessel **9** where it expands to cause the supercritical fluid to separate as a gas from the liquid vehicle. The gas may be fed by conduit **18** to a tank **10** and returned by conduit **19** to the cooler **2**. The vehicle may also be collected for subsequent re-use. Means, not shown, may be provided to smooth the flow pulse of fluids and vehicles produced by pumps **3** and **4**, so as to eliminate, or at least reduce, any flow pulsations.

When sufficient particle formation has occured in the vessel **6**, it is flushed through with clean, dry supercritical fluid, so as to ensure removal of any residual vehicle. The vessel can then be depressurised and particulate product removed.

The alternative apparatuses shown schematically in Figures 24A and 24B are for use in continuous particle formation. That shown in Figure 24A includes two particle formation vessels **6a** and **6b**, each of the type shown in Figure 1 and each including an inlet nozzle **20** and a particle collecting means (such as a filter) **21**. Oven **7** serves both vessels.

In the apparatus in Figure 24A, valve **A** controls the supply of the supercritical fluid and the vehicle (containing the substance of interest) to the two vessels **6a** and **6b**, and one-way valves **E** and **F** control the outlets from the two vessels to the back-pressure regulator **8**. Valve **D** controls the supply of the vehicle to valve **A**. Valves **B** and **C** are needle valves, and items **80** and **81** are vents.

The apparatus may be "continuously" operated as follows. Valve **A** is firstly set to supply fluids to vessel **6a**, in which particle formation is allowed to occur, as described in connection with Figure 1. Valve **E** is set so that the resultant supercritical solution may drain from vessel **6a** to the back-pressure regulator **8** for subsequent recycling.

When sufficient particle formation has occurred, valve **D** is closed to stop the flow of vehicle, whilst the supercritical fluid continues to flow through vessel **6a** to dry (flush) the products. Valve **A** is then set to supply fluids to the empty vessel **6b** and valve **D** re-opened, whilst valve **B** is opened so as slowly to depressurise vessel **6a**. One-way valve **E** eliminates any chance of a back-flow

from vessel **6b** or of disruption of the particle formation process now occurring in vessel **6b**. Vessel **6a** is removed for collection of the product, and then refitted and repressurised ready for re-use. Supercritical solution drains from vessel **6b** via valve **F**, which is set appropriately.

Once particle formation in vessel **6b** is complete, the valves are set back to allow it to continue in vessel **6a**, whilst **6b** is flushed and emptied. In this way, particle formation in the apparatus can continue uninterrupted.

The apparatus shown in Figure 24B includes only one particle formation vessel **6**, which does not contain any particle collecting means, and two particle collection vessels **25a** and **25b** downstream of vessel **6**. The supercritical fluid carries the formed particles to the collection vessels **25a** and **25b**.

The apparatus also includes an inlet nozzle **20**, two vents **26**, a back pressure regulator **27**, an oven **7** and valves **A - H**. Supercritical fluid and solution (vehicle) are fed to the nozzle **20** where shown.

The apparatus might be used as follows. Initially, (valves **C, D, E**, and **F** closed) the system is pressurised and stable working conditions are met; valves **B** and **H** are then closed, driving the flow of supercritical fluid through valve **A** only. The vehicle and substance of interest are introduced into vessel **6** and the particles formed are transported by the supercritical fluid via valve **A** to collection vessel **25a** which contains a particle retention device. The retention device is placed at the outlet of the vessel to ensure maximum collection volume. The solid-free supercritical solution (the supercritical fluid and the vehicle) flows across valve G to the back pressure regulator **27**. On emerging from the back pressure regulator the supercritical solution expands into a large pressure resistant vessel (not shown), where the vehicle separates from the gas and both can be recycled.

When the collection vessel **25a** is full, switching takes place, closing valves **A** and **G** and simultaneously opening valves **B** and **H**. This allows the flow of the supercritical solution, emerging from vessel **6**, into the second collection vessel **25b**. Valves **C** and **G** are opened after flow switching to ensure a high flow of supercritical fluid to flush the full collection vessel **25a**, i.e. the supercritical solution volume is replaced by a supercritical fluid volume. It is estimated that 1-2 times the voume of the collection vessel, of the supercritical fluid, ensures a

dry powder. The flushing time is generally short owing to the fact that the particles are occupying the volume of the collection vessel. After flushing, valves **C** and **G** are closed and valve **F** (a needle valve) is slowly opened to depressurise the full collection vessel **25a**. Since the particulate product takes up the vessel volume only a small amount of supercritical fluid is discharged, mainly the internal volume of the fittings involved.

The full collection vessel **25a** is removed and the dry powder collected. After refitting and repressurising via valve **C**, the vessel is ready for re-use as soon as the second collection vessel **25b**, which has meantime been collecting product from vessel **6**, is full.

The benefits of using the apparatus of Figure 24B include:

1. The elimination of depressurising and pressurising steps of the reaction vessel every time product is collected. This could mean considerable reductions in the amounts of fluids being discharged, in particular when using a large volume particle formation vessel (scaling up) or expensive high purity gases.

2. Significant time saving during the flushing (drying) procedure. In a batch particle formation process only a rather small volume of the reaction vessel is occupied by the product and the remaining volume (where dispersion takes place) is taken up by the supercritical solution. This mixture will eventually be replaced by at least the same volume of the supercritical fluid in the flushing procedure, which can therefore take a long time when scaled up.

3. The environment and workers are less exposed to the products during the recovery step. In some cases it is difficult to collect products directly from a large reaction vessel due to handling inconvenience or because the products of interest are light, oxygen or humidity sensitive which might affect their characteristics or purity.

The invention is further illustrated by the following non-limiting examples. Examples 1 to 5, illustrating the preparation of salmeterol xinafoate and its physical properties were carried out using apparatus substantially the same as

that illustrated in Figures 1 and 2, using a 32ml particle formation vessel and a two-passage coaxial nozzle having the following dimensions:

	outer diameter	inner diameter
outer tube:	1.58mm	0.75mm
inner tube:	0.63mm	0.20mm

The tip orifice (**43** in Figure 2B) was 0.32mm in diameter, and both the inner and outer tubes were made of stainless steel.

Example 1

Conventionally crystallised salmeterol xinafoate, both before and after micronisation, was compared against salmeterol xinafoate of the present invention. A solution of salmeterol xinafoate in acetone (0.63%$^{w}/_{v}$) was co-introduced with CO_2 at 300 bar and 45°C via a coaxial nozzle into the particle formation vessel using the apparatus described and shown in Figure 1 to give sample 1. A solution of salmeterol xinafoate in acetone (0.50%$^{w}/_{v}$) was cointroduced with CO_2 at 100 bar and 55°C via a coaxial nozzle into the particle formation vessel using the apparatus described and shown in Figure 1 to give sample 2. In each case, the solution flow rate was 0.4ml/min and supercritical CO_2 was co-introduced into the particle formation vessel at a flow rate of 9ml/min.

The dynamic bulk densities are shown below in Table 2:

Table 2

Sample	Dynamic Bulk Density W ($g.cm^{-3}$)
conventionally crystallised salmeterol xinafoate (non-micronised)	0.312
conventionally crystallised salmeterol xinafoate (micronised)	0.137
salmeterol xinafoate of the present invention (sample 1)	0.033
salmeterol xinafoate of the present invention (sample 2)	0.059

The conventionally crystallised salmeterol xinafoate was prepared using the methodology described in International Patent Specification No. WO 92/09557.

Example 2

Control of Formation of the Polymorphs of Salmeterol Xinafoate

A solution of salmeterol xinafoate in methanol (0.6% w/v) was co-introduced with CO_2 at 300bar and 45°C via a coaxial nozzle into the particle formation vessel using the apparatus described and shown in Figure 1. A dry, easily handlable powder without significant static charge was formed. The product was characterised by differential scanning calorimetry (DSC) and by X-ray powder diffraction (XRD), and data are shown in Figures 4 and 5. A highly crystalline product with well defined melting point (peak heat flow = 123.5°C) was obtained. Major intensities in the XRD pattern were observed at 4.2, 17.3, and 24.5 degrees 2 theta. This material was defined as Polymorph I.

In another experiment, a solution of salmeterol xinafoate in acetone (0.6% w/v) was co-introduced with CO_2 at 250 bar and 90°C via a coaxial nozzle into the particle formation vessel using the apparatus described and shown in Figure 1. A dry, easily handlable powder without significant static charge was formed. The data from DSC and XRD are shown in Figures 6 and 7. A second polymorph was obtained, defined as Polymorph II. This form was crystalline with a well defined melting point (peak heat flow = 135.8°C). A different XRD pattern from Polymorph I was obtained with a new major intensity at 2.9 degrees 2 theta. The change in working conditions led to the formation of a pure, higher melting point phase (Polymorph II) which had previously only been observed, in prior known methods of preparing salmeterol xinafoate, after heating Polymorph I at temperatures which caused heat induced transition.

Controlled formation of mixtures of Polymorph I and Polymorph II was also achieved by varying the working conditions. DSC and XRD data (see Figures 8 to 11) confirm the mixed phase status of these products with increasing Polymorph II component as the working temperature was increased.

Example 3

Control of Particle Size and Size Distribution

A solution of salmeterol xinafoate in acetone (0.6% w/v) was co-introduced with CO_2 at 200 bar and 55°C via a coaxial nozzle into the particle formation vessel using the apparatus described and shown in Figure 1. A series of products

was obtained by changing the flow rate ratio of salmeterol xinafoate solution/supercritical CO_2, where the flow ratio is defined as:

$$\frac{\text{(flow rate of vehicle containing the solute)}}{\text{(flow rate of supercritical fluid)}}$$

The flow ratio was changed between 0.01 and 0.07, with a flow rate of 9ml/min for the supercritical CO_2.

The resultant dry, easily handlable products without significant static charge were examined by scanning electron microscopy (SEM) and by laser diffraction (Malvern Mastersizer E) for particle size analysis (see Figures 12-15). It was found that by decreasing the flow rate ratio of salmeterol xinafoate solution/supercritical CO_2, finer particles were obtained (see Figures 12 and 13) than for higher fluid flow rate ratios (see Figures 14 and 15). The particle size analysis data is shown in Table 3 below.

Table 3

	Mean Particle Size (μm)	%<5μm	%<10μm	Uniformity Index
Conventionally crystallised salmeterol xinafoate (micronised)	1-3	Typically >90	Typically >95	13.1
Salmeterol xinafoate of the present invention (sample 1)	3.85	66.0	94.5	10.2
Salmeterol xinafoate of the present invention (sample 2)	18.84	5.7	16.1	19.2

The uniformity index is defined as:-

$$100 \times \left[\frac{\text{particle size at 10\% cumulative undersize}}{\text{particle size at 90\% cumulative undersize}} \right]$$

In another experiment, a solution of salmeterol xi of salmeterol xinafoate in isopropanol w/v) was co-introduced with CO_2 at 150 bar and 60°C via a coaxial nozzle into

the particle formation vessel using the apparatus described and shown in Figure 1. The dry, easily handlable product without significant static charge was examined by SEM (see Figure 16) and found to be composed of needle shaped particles with a maximum particle dimension of up to 300 microns.

Thus by controlling and changing the working conditions of the particle formation process, salmeterol xinafoate products composed of particles with different particle sizes and size distributions were produced.

Example 4

Control of Particle Shape

A solution of salmeterol xinafoate in 96% ethanol (0.8 w/v) was co-introduced with CO_2 at 300 bar and either 50°C or 60°C via a coaxial nozzle into the particle formation vessel using the apparatus described and shown in Figure 1. The dry, easily handlable products without significant static charge were examined by SEM. The product obtained at 50°C was composed of blade-like shaped particles with reduced elongation (See Figure 17) compared with the acicular, needle shaped particles produced at 60°C. (See Figure 18).

In another experiment, a solution of salmeterol xinafoate in acetone (0.6% w/v) was co-introduced with CO_2 at 200 bar and 50°C via a coaxial nozzle into the particle formation vessel using the apparatus described and shown in Figure 1. The dry, easily handlable products without significant static charge was examined by SEM (see Figure 19) and particles were found to be plate-like microcrystalline accretions.

Thus by controlling the working conditions of the particle formation process, salmeterol xinafoate products composed of particles having different particle shapes can be produced.

Example 5

Formation of Particles with Salmeterol Xinafoate Deposited onto a Solid Substrate

A solution of salmeterol xinafoate in methanol (0.6% w/v) also containing a dispersion of silicon dioxide fumed B.P. (0.06%w/v) was co-introduced with CO_2 at 300 bar and 45°C via a coaxial nozzle into the particle formation vessel using the apparatus described and shown in Figure 1. A second methanol solution, as above, but without dispersed silicon dioxide fumed B.P. was similarly

co-introduced, into the particle formation vessel under equivalent working conditions. The resultant dry, easily handlable powdered products without significant static charge were examined by differential scanning calorimetry (DSC) (see Figures 20 and 21) and X-ray power diffraction (XRD) (see Figures 22 and 23). The DSC profile for the sample with salmeterol xinafoate deposited onto the silicon dioxide fumed particles (Figure 20) showed a wider melting endotherm with a lower peak heat flow temperature than that for the salmeterol xinafoate sample without silicon dioxide fumed prepared under equivalent conditions (Figure 21). The XRD pattern for the sample with salmeterol xinafoate deposited onto the silicon dioxide fumed particles (Figure 22) exhibited reduced crystallinity as indicated by the reduction in measured intensity valves than that for the salmeterol xinafoate sample without silicon dioxide fumed prepared under equivalent conditions (Figure 23).

These data indicate the deposition of salmeterol xinafoate onto the silicon dioxide fumed particle substrates with changes in the degree of crystallinity of salmeterol xinafoate, compared with samples of salmeterol xinafoate prepared under equivalent working conditions without silicon dioxide fumed particles as a solid substrate.

Example 6

Use of Larger Scale Apparatus

Figures 26 and 27 A - F show the construction of a relatively large-scale particle formation vessel **90** which may be used in apparatus as described herein. The vessel includes an inner reaction chamber **91** and vessel wall **92** and a screw-threaded end cap **93** engageable with the upper end of wall **92**. A lid **94** has a central opening **95** for a nozzle assembly and a peripheral opening **96** for an outlet, which will contain a particle retaining device (e.g. a filter).

In the Figure 27, A - C show the main vessel with its vessel wall **92**; D shows the end cap **93**; E shows the lid **94** and F an O-ring seal **97** used to seal the upper end of the reaction chamber **91**. Dimensions in mm are shown for the various components.

Vessel **90** was used with a two-passage nozzle to produce salmeterol xinafoate. Operating conditions were a 1.25% w/v solution of salmeterol xinafoate in acetone, at 100 bar and 60°C. Two SEM photographs (Figures 28 and 29) and

an X-ray powder diffraction pattern (Figure 30) are provided for the sample obtained.

Clearly, the process described herein may be carried out using relatively large-scale apparatus and still be effective in the controlled formation of particle products.

Example 7

Effect of Operating Conditions on Particle Size

The process was carried out in a similar manner to that described in Examples 1 - 5, using a particle formation vessel of 50ml capacity and a two-passage nozzle, in order to produce particles of salmeterol xinafoate. The effects of changing temperature, pressure and supercritical fluid flow rate, on the mean size of the product particles, were investigated. The results are shown in Figures 31 - 33.

Figure 31 is a graph of mean particle size diameter (microns), measured using the Malvern sizing technique, versus temperature (°C) in the particle formation vessel. The salmeterol xinafoate was precipitated at 300 bar from acetone. The quoted flow rates represent acetone/salmeterol solution flow rates at a constant CO_2 flow of 9 ml/min.

Figure 32 shows the effect of vessel pressure on particle size at four different temperatures. Flow rates were 0.1 ml/min for the acetone solution and 9 ml/min for the CO_2.

Figure 33 shows a graph of CO_2 ("SF") flow rate versus particle size, the salmeterol xinafoate being precipitated from acetone at an acetone/ salmeterol solution flow rate of 0.3 ml/min and a 1.25% w/v concentration. The operating temperature was 60°C, the pressure 120 bar.

Example 8

Use of Three-Passage Nozzle

The above examples were all carried out using apparatus similar to that shown in Figure 1, and a two-passage inlet nozzle of the type shown in Figures 2A and 2B. In contrast, the present example was carried out using a three-passage inlet nozzle of the type shown in Figure 25, having the following dimensions:

	External diameter	Internal diameter
Outer tube **70**	1.54 mm	0.75 mm
Intermediate tube **60**	0.70 mm	0.35 mm
Inner tube **50**	0.30 mm	0.15 mm

Nozzle opening: 0.22 mm internal diameter.

All tubes of the nozzle were made of stainless steel. The particle formation vessel used had a capacity of 32ml.

A sample of salmeterol xinafoate was prepared from a 0.5% w/v acetone solution at 200 bar and 50°C, using an acetone/salmeterol solution flow rate of 0.2 ml/min through the intermediate nozzle passage, and a CO_2 flow rate through the inner and outer nozzle passages of 5 ml/min. Figure 34 shows X-ray data for the sample obtained.

Example 9

Reduced Static Charge - salmeterol xinafoate

Using samples prepared as described in Example 1, a simple test was devised to determine their relative static charge based on the quantity of drug remaining coated to the walls of a vial after rolling a predetermined quantity of drug in the vial for 5 minutes. The greater the drug remaining on the vial, the higher the relative static charge associated with the drug substance. Results are shown in Table 4.

Table 4

Sample	% Drug Retaining on Vial
Conventionally crystallised salmeterol xinafoate (micronised)	7.0
Salmeterol xinafoate of present invention, sample 1	2.5
Salmeterol xinafoate of present invention, sample 2	5.7

The results indicate a lower relative static charge for the salmeterol xinafoate of present invention compared to conventionally crystallised salmeterol xinafoate (micronised). In contrast to conventionally crystallised salmeterol xinafoate, the salmeterol xinafoate of the present invention has no significant static charge when first formed. The lower relative static charge has several advantages; improved flow properties, improved fluidisability and better drug deposition in the lungs from dry powder formulations.

Example 10

Preparation of a Salmeterol Xinafoate and Polymer Matrix

An acetone solution containing 0.45% w/v of salmeterol xinafoate and 0.05% w/v hydroxypropylcellulose (Klucel SL) was prepared and fed into apparatus similar to that shown in Figure 1, using a two-passage nozzle and a 50ml particle formation vessel. The operating conditions were 120 bar and 60°C, with flow rates of 0.4 ml/min for the salmeterol/polymer solution and 9 ml/min for the supercritical CO_2. A fine, white powder containing 10% w/w hydroxypropylcellulose in salmeterol xinafoate was obtained as a product.

A product of similar appearance, but containing 20% w/w hydroxypropylcellulose, was also prepared from a second solution, using the same operating conditions as for the first product.

Figures 35 and 36 are X-ray powder diffractogram profiles for the first and second samples respectively. Increasing disturbance of the crystalline salmeterol xinafoate can be seen with increasing hydroxypropylcellulose content, confirming the inclusion of the polymer matrix material into the sample.

This example thus illustrates how the process described may be used to prepare multi-component particles containing salmeterol xinafoate in a polymer matrix. The incorporated second component may be a pharmaceutically acceptable carrier such as a polymer (e.g. starch or hydroxypropylcellulose), silicon dioxide, sorbitol, mannitol or lactose. It may be used to modify the dissolution performance or other properties of a drug.

Example 11

Reproducibility

Two different solutions of salmeterol xinafoate in acetone (0.6%w/v) were made and each solution was co-introduced with CO_2 via a coaxial nozzle into the

particle formation vessel using the apparatus described on two different days to give samples A and B. The operating conditions were 300 bar and 35°C, with flow rates of 0.2ml/min for the salmeterol solution and 6ml/min for the supercritical CO_2. The crystallised salmeterol xinafoate provided from each solution was examined for particle size, size distribution, crystal shape and twin impinger performance.

a) Particle size and distribution

The particle size and distribution was determined by laser diffraction (Malvern Mastersizer), see Table 5.

Table 5

	Mean Particle Size (Microns)	% <5 microns	% <10 microns	Uniformity Index
Sample A	7.2	31.6	67.8	9
Sample B	7.7	28.3	64.5	9

b) Crystal shape

The crystal shape was examined by SEM, see Figures 37 and 38.

c) Twin Impinger Performance

A small quantity of drug was filled into each blister of a 4-blister dry powder pack (Rotadisk™). The contents of each blister were emptied, via a dry powder inhaler device (Diskhaler™), into the Twin Impinger apparatus set to an airflow rate of 60 litres per minute. Each stage of the Twin Impinger apparatus contained a quantity of dissolving agent, methanol, (stage 1, 7ml and stage 2, 30ml). The blister and the inhaler device were washed with methanol and the resultant solution made up to 50ml. The stage 1 of the Twin Impinger apparatus was washed with methanol and the resultant solution made up to 100ml. The stage 2 of the Twin Impinger apparatus was washed with methanol and the resultant solution made up to 100ml. The solutions were diluted by 10:1 with methanol. The diluted solutions were assayed by UV spectrophotometry and the quantity of drug delivered to each stage of the Twin Impinger apparatus was calculated. The results are shown in Table 6.

Table 6

Sample	Drug Deposition as a % of Total Drug Recovered.		
	Device	Stage 1	Stage 2
Conventionally crystallised salmeterol xinafoate (micronised)	17.0	72.8	10.2
Salmeterol xinafoate of present invention, sample A	24.4	57.6	18.0
Salmeterol xinafoate of present invention, sample B	20.7	56.2	23.1

The stage 2 deposition represents the fine particle mass (respirable dose) reaching the deep lung. Salmeterol xinafoate of the present invention shows superior stage 2 deposition. This indicates the improved flow properties, fluidisability and reduced static of the supercritical fluid crystallised salmeterol xinafoate.

The interesting feature of the present invention is that the supercritically fluid crystallised salmeterol xinafoate with a particle size greater than that of conventionally crystallised salmeterol xinafoate (micronised) gives higher deposition (respirable dose) in the stage 2 of the Twin Impinger.

The results from the particle size analysis, crystal shape and Twin Impinger show that the process is essentially reproducible when using the same crystallising parameters.

Example 12

Enhancement of Purity of a Particulate Product

This example shows how the method described herein may be used to enhance the purity of the particulate product, on precipitation of the product from a solution containing impurities.

0.2022 g of salmeterol xinafoate was mixed with 0.0242 g of salicylic acid, analar grade (BDH Chemicals Ltd, UK) (the "impurity"), dissolved in 60ml of absolute ethanol and fed to a 50ml particle formation vessel through a two-

passage nozzle. The operating conditions were 200 bar and 50°C; a solution (10.69% w/w salicylic acid in salmeterol) flow rate of 0.3 ml/min; and a supercritical CO_2 flow rate of 9 ml/min.

The product, a white fluffy powder, was collected and analysed using HPLC. The analysis was carried out utilising a Pye Unicam*PU4015 HPLC system (Pye Unicam Ltd, UK), and a column 150 x 4.6 mm packed with 5 micron Spherisorb* ODS2 (Jones Chromatography, UK). The mobile phase consisted of acetonitrile, 0.1M aqueous ammonium acetate and 0.1M aqueous sodium dodecyl sulphate (52:24:24 v/v) and the pH was adjusted to 3.8 with glacial acetic acid. The flow rate of the mobile phase was 2.0 ml/min. The injection volume of the sample solutions prepared (5mg/ml $\pm$ 0.5 mg concentration) was 20 µl and the UV detector was set at 278 nm and the integrator (Hewlett Packard HP3394A) at an attenuation of 8.

Figure 39 is an HPLC chromatogram for the pure salmeterol xinafoate used in the experiment. Figure 40 is an HPLC chromatogram for the pure salicylic acid used. Figure 41 is an HPLC chromatogram for the salmeterol/salicylic acid solution fed into the particle formation vessel, and Figure 42 an HPLC chromatogram for the product obtained through carrying out the method of the invention.

Figures 41 and 42 reveal a significant improvement in the purity of the salmeterol xinafoate and an important reduction in the salicylic acid concentration from 10.69% w/w to less than 0.8% w/w. This confirms the ability of the technique described herein to extract, selectively, one or more impurities from a sample and hence to enhance the purity of a desired particulate product.

Example 13

Preparation of Lactose

In this example, the method was used to prepare lactose, but using two vehicles instead of one. Lactose is a water-soluble sugar, but water would be unsuitable as the only vehicle because it is insoluble in, and hence could not be extracted into, supercritical CO_2. Instead, a solution of lactose in a relatively small amount of water and a relatively large amount of a second vehicle, methanol, which is both miscible with water and soluble in supercritical CO_2, was used. The solution was introduced with supercritical CO_2 through a three-passage nozzle. It is thought that the miscible water and methanol are extracted together

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into the supercritical CO_2, despite the insolubility of water in the supercritical fluid.

0.3 g of alpha-lactose monohydrate was dissolved in 2 ml de-ionised water, 98 ml of methanol was added to the aqueous solution and introduced into a 32 ml particle formation vessel through a three-passage nozzle. The operating conditions were 270 bar and 70°C, a solution flow rate (in the intermediate nozzle passage) of 0.5 ml/min and a supercritical CO_2 flow rate (in the inner and outer passages) of 7.5 ml/min. The product (a fine white powder) was collected at the end of the experiment. An SEM micrograph and XRD pattern for the product are shown in Figures 43 and 44 respectively.

In another similar experiment, a 0.5% w/v solution of alpha-lactose monohydrate in methanol: water (95:5 $^{v}/_{v}$) was prepared and delivered to a 50 ml high pressure particle formation vessel via a two-passage nozzle. The working conditions were 150 bar and 50°C , with a flow rate of 0.7 ml/min for the solution and 9 ml/min for the supercritical CO_2. The collected product was a free flowing, fine white powder Figures 45 and 46 show an SEM micrograph and XRD pattern receptively for this product.

The SEM micrographs reveal a marked difference in the shape of the alpha-lactose particles prepared under the different operating conditions. The XRD patterns indicate the crystalline nature of the products.

Lactose is commonly used as a carrier for pharmaceuticals, in particular for drugs to be delivered by inhalation methods. It is thus extremely useful to be able to use the method described herein to prepare lactose particles in a controlled manner, despite the difficulty of dissolving lactose in organic solvents.

<u>Example 14</u>

<u>Preparation of a Salmeterol Xinafoate and Polymer Matrix (Alternative Method).</u>

A similar experiment to Example 10 was carried out, but using a three-passage nozzle to co-introduce separate solutions of the salmeterol xinafoate and hydroxypropylcellulose, so as to allow mixing of the two components immediately prior to particle formation.

Two separate solutions in acetone were prepared: hydroxypropylcellulose (Klucel SL) at 0.05% w/v and salmeterol xinafoate at 0.45% w/v. These were co-introduced with supercritical CO_2 into a 32ml particle formation vessel. The working conditions were 120 bar and 60°C. The flow rates were 9 ml/min for the CO_2 (inner nozzle passage); 0.2 ml/min for the polymer solution (intermediate passage); and 0.2 ml/min for the salmeterol solution (outer passage).

This use of the three-passage nozzle allows the two reactants (drug and polymer) to be rapidly mixed in situ prior to their dispersion by the supercritical fluid.

A white fluffy powder was obtained as a product. A product of similar appearance was obtained using a 0.1% w/v solution of hydroxypropylcellulose and a 0.4% w/v solution of salmeterol xinafoate. Figures 47 and 48 are XRD patterns for the first and second products respectively. Increasing disturbance of the crystalline salmeterol xinafoate can be seen with increasing polymer content, confirming the inclusion of the polymer matrix material into the product.

The XRD patterns are comparable to those obtained in Example 10. This supports the belief that rapid mixing of the two materials takes place in situ, before dispersion by the supercritical fluid, when using the three-passage nozzle in this way.

The above examples show how the apparatus and method described herein can be used to produce particles of a pharmaceutical produced in a controlled manner. However, it will be appreciated that the apparatus and processes can have much wider applications, for instance:

- to produce particles of products of controlled size and shape for use in the pharmaceutical, photographic, ceramics, explosives/propellants, dye and food industries and others, especially products which decompose or are otherwise compromised when subjected to conventional particle formation and milling techniques.

- to produce solid, stable forms of molecules and macromolecules which are difficult to process/freeze dry (e.g. proteins, peptides and polymers generally).

- to produce a particular polymorphic form of a compound or to separate and/or enrich mixtures of isomers (including optical isomers) or polymorphs.

- to purify drugs and other products, by removal of trace impurities (including solvents) using controlled selective precipitation (i.e. using the invention to precipitate the impurities themselves).

- to coat substrates in a controlled manner, including with thin film liquid coatings.

- to control "doping" of compounds in products based on crystal lattices or to produce intimate blends of two or more products.

- to prepare completely new phases or materials under conditions not achievable using conventional particle formation techniques.

We claim:

1. 4-Hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol (salmeterol), 1-hydroxy-2-naphthalenecarboxylate (xinafoate) in an easily handled and easily fluidised crystalline form, with a dynamic bulk density of less than 0.1 $g.cm^{-3}$.

2. Salmeterol xinafoate as claimed in claim 1 with a dynamic bulk density in the range between 0.01 and 0.075 $g.cm^{-3}$.

3. Salmeterol xinafoate as claimed in claim 1 or claim 2 which has a particle size in the range of 1 to 10 microns.

4. Salmeterol xinafoate as claimed in any one of claims 1 to 3 which has a uniformity coefficient of from 1 to 20.

5. Salmeterol xinafoate as claimed in any one of claims 1 to 4 which has a respirable fraction of 14% or more by weight.

6. Salmeterol xinafoate as claimed in any one of claims 1 to 5 which has a respirable fraction of 15 to 30% by weight.

7. Salmeterol xinafoate as claimed in any one of claims 1 to 6 which has a cohesivity of 0 to 20%.

8. Salmeterol xinafoate as claimed in any one of claims 1 to 7 which has a cohesivity of 0 to 5%.

9. Salmeterol xinafoate as claimed in any one of claims 1 to 8 in the form of pure Polymorph I characterised by a single differential scanning calorimetry endotherm at about 123.5°C.

10. Salmeterol xinafoate as claimed in any one of claims 1 to 8 in the form of pure Polymorph II characterized by a single differential scanning calorimetry endotherm at about 135.8°C.

11. A pharmaceutical composition comprising salmeterol xinafoate as claimed in any one of claims 1 to 10 together with a pharmaceutically acceptable carrier.

12. A pharmaceutical composition as claimed in claim 11 wherein the carrier is silicon dioxide or hydroxypropylcellulose.

13. A pharmaceutical composition as claimed in claim 11 wherein the carrier is lactose.

14. A pharmaceutical composition as claimed in claim 13 in the form of a dry powder suitable for inhalation.

15. A pharmaceutical composition as claimed in any one of claims 11 to 14 the form of multicomponent particles comprising salmeterol xinafoate and carrier.

Fig.1.

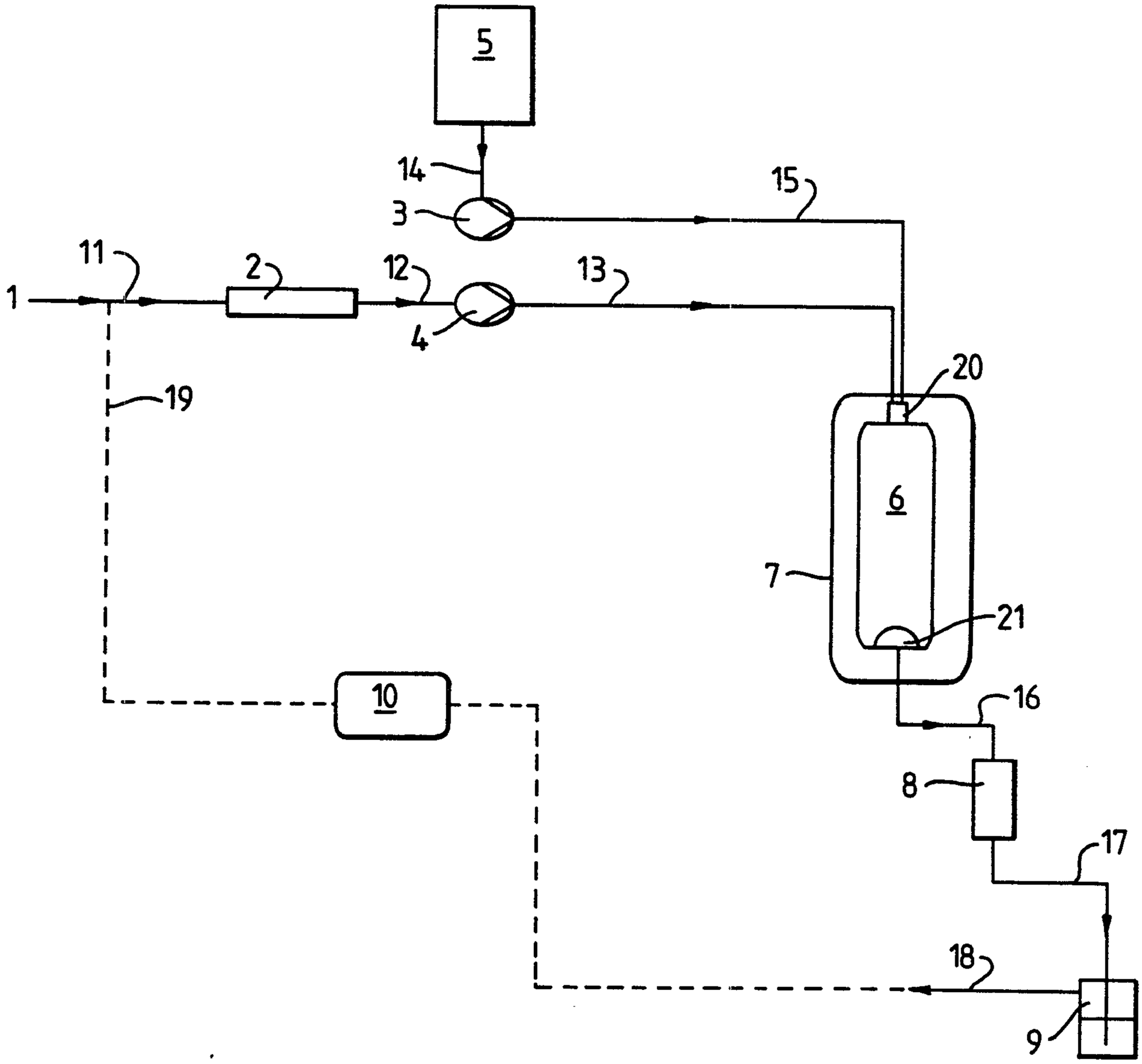


Fig.2A.

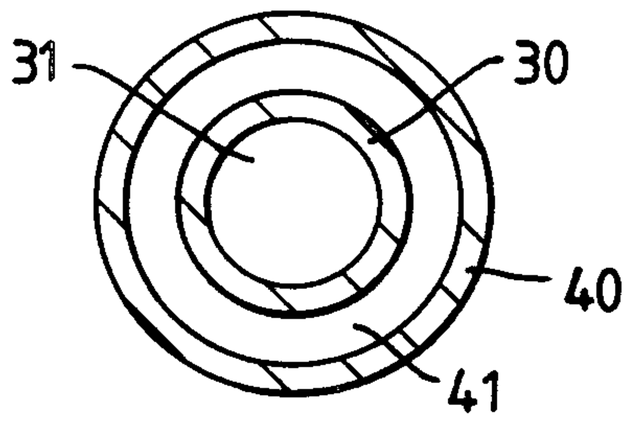
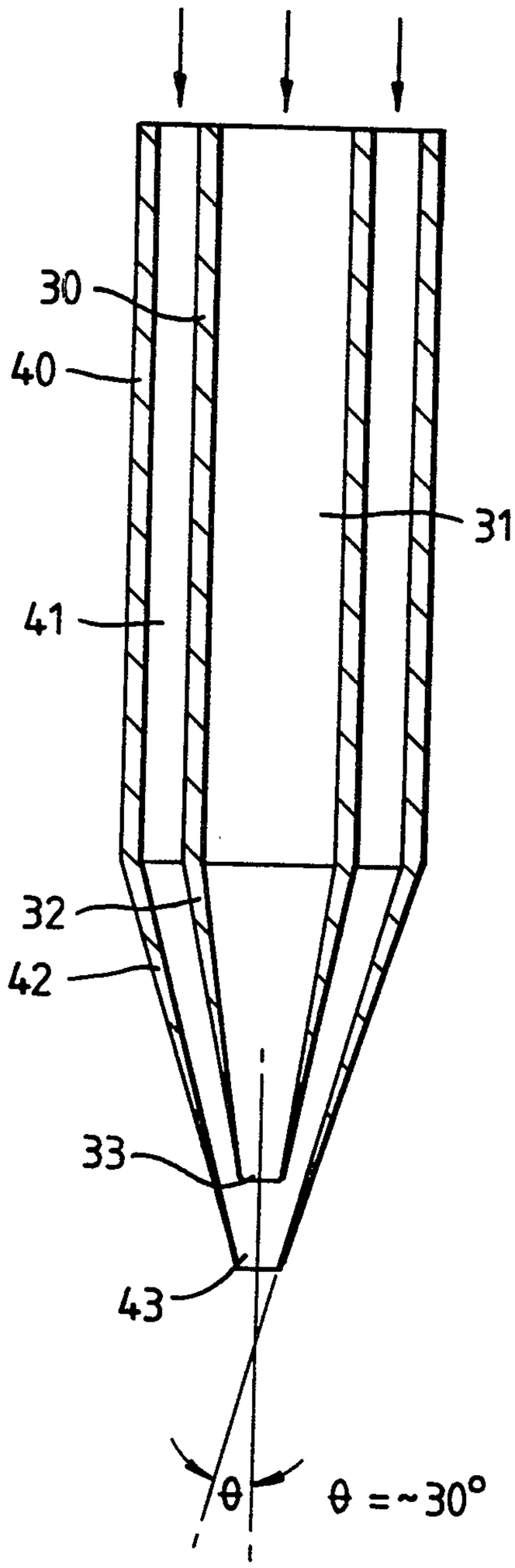


Fig.2B.



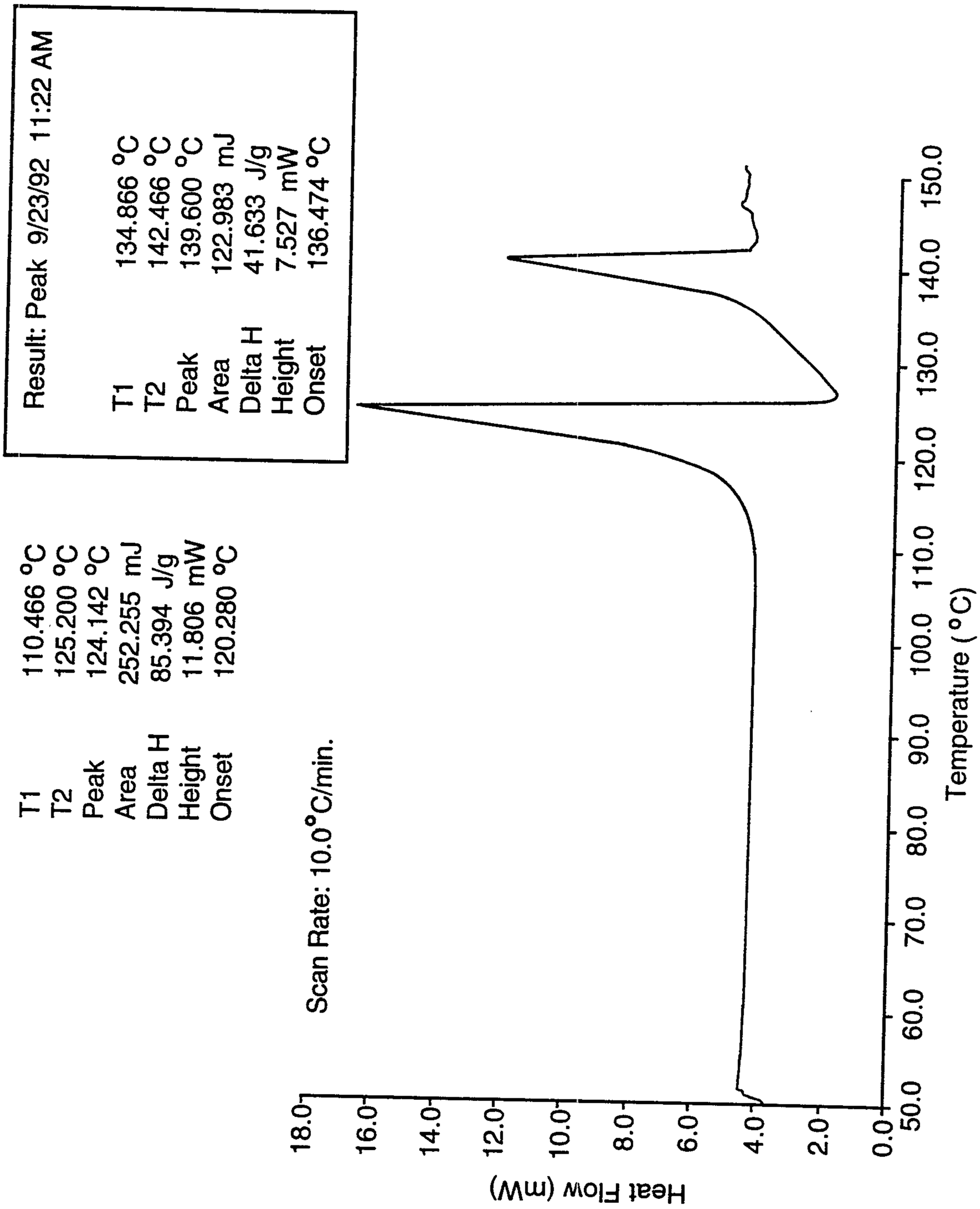

Result: Peak 9/23/92 11:22 AM
T1 134.866 °C
T2 142.466 °C
Peak 139.600 °C
Area 122.983 mJ
Delta H 41.633 J/g
Height 7.527 mW
Onset 136.474 °C
PERKIN- ELMER
7 Series Thermal Analysis System
T1 110.466 °C
T2 125.200 °C
Peak 124.142 °C
Area 252.255 mJ
Delta H 85.394 J/g
Height 11.806 mW
Onset 120.280 °C
Scan Rate: 10.0°C/min.
Heat Flow (mW)
18.0
16.0
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
Temperature (°C)

Fig.3.

Fig.4.

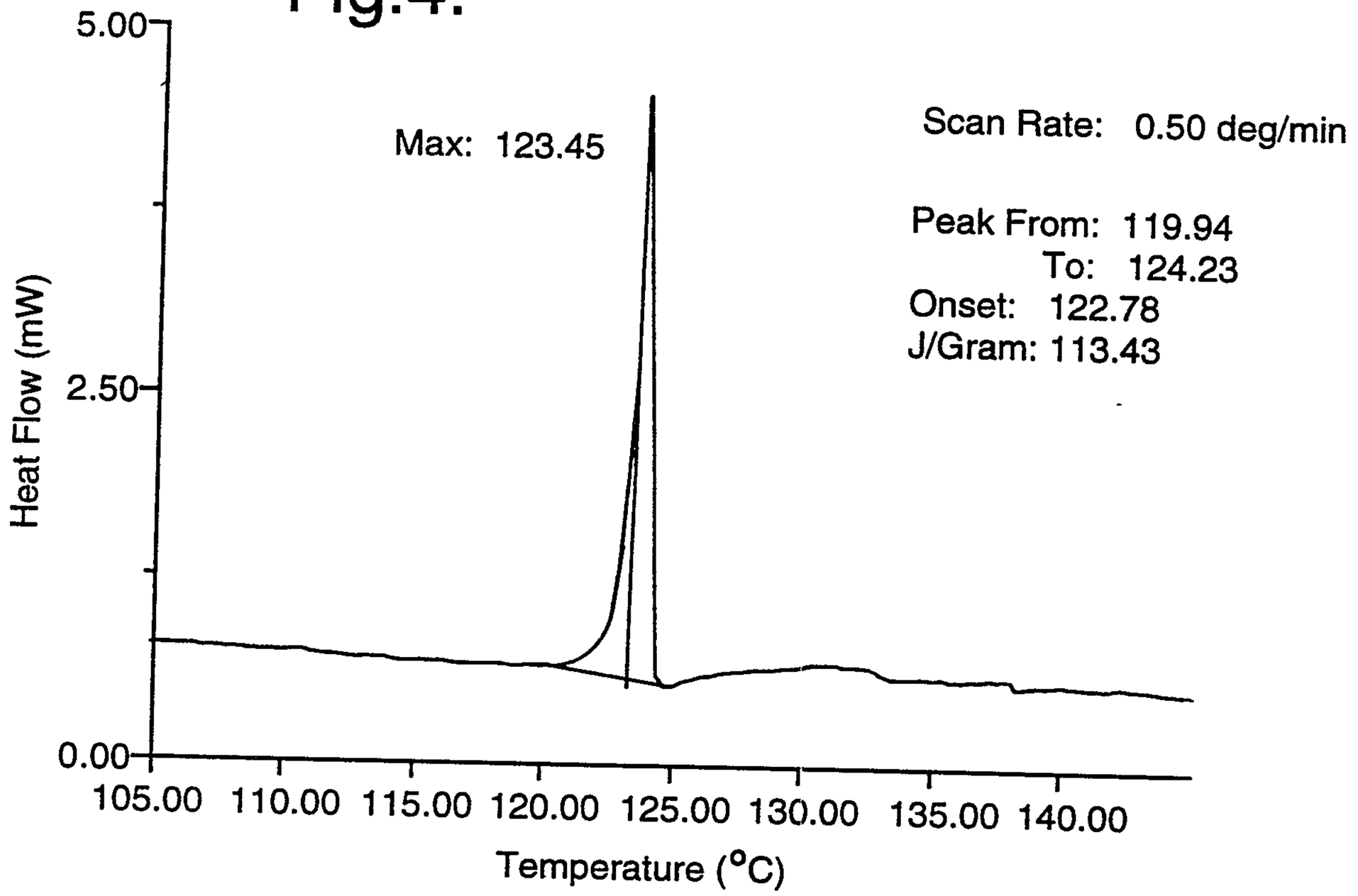

5.00
2.50
0.00
Heat Flow (mW)
105.00
110.00
115.00
120.00
125.00
130.00
135.00
140.00
Temperature (°C)
Max: 123.45
Scan Rate: 0.50 deg/min
Peak From: 119.94
To: 124.23
Onset: 122.78
J/Gram: 113.43

Fig.5.

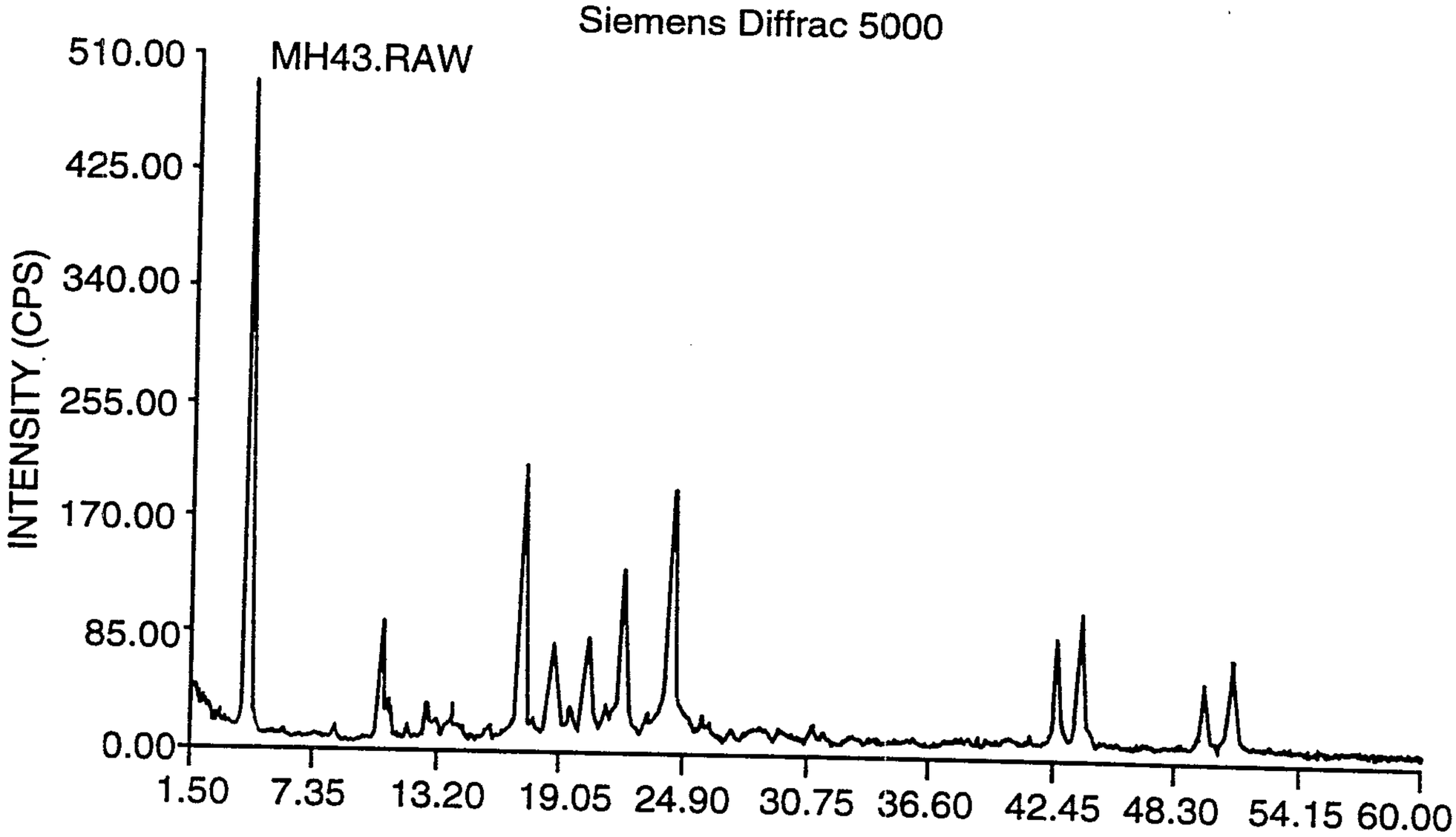

Siemens Diffrac 5000
MH43.RAW
510.00
425.00
340.00
255.00
170.00
85.00
0.00
INTENSITY (CPS)
1.50
7.35
13.20
19.05
24.90
30.75
36.60
42.45
48.30
54.15
60.00
Two - Theta

Fig.6.

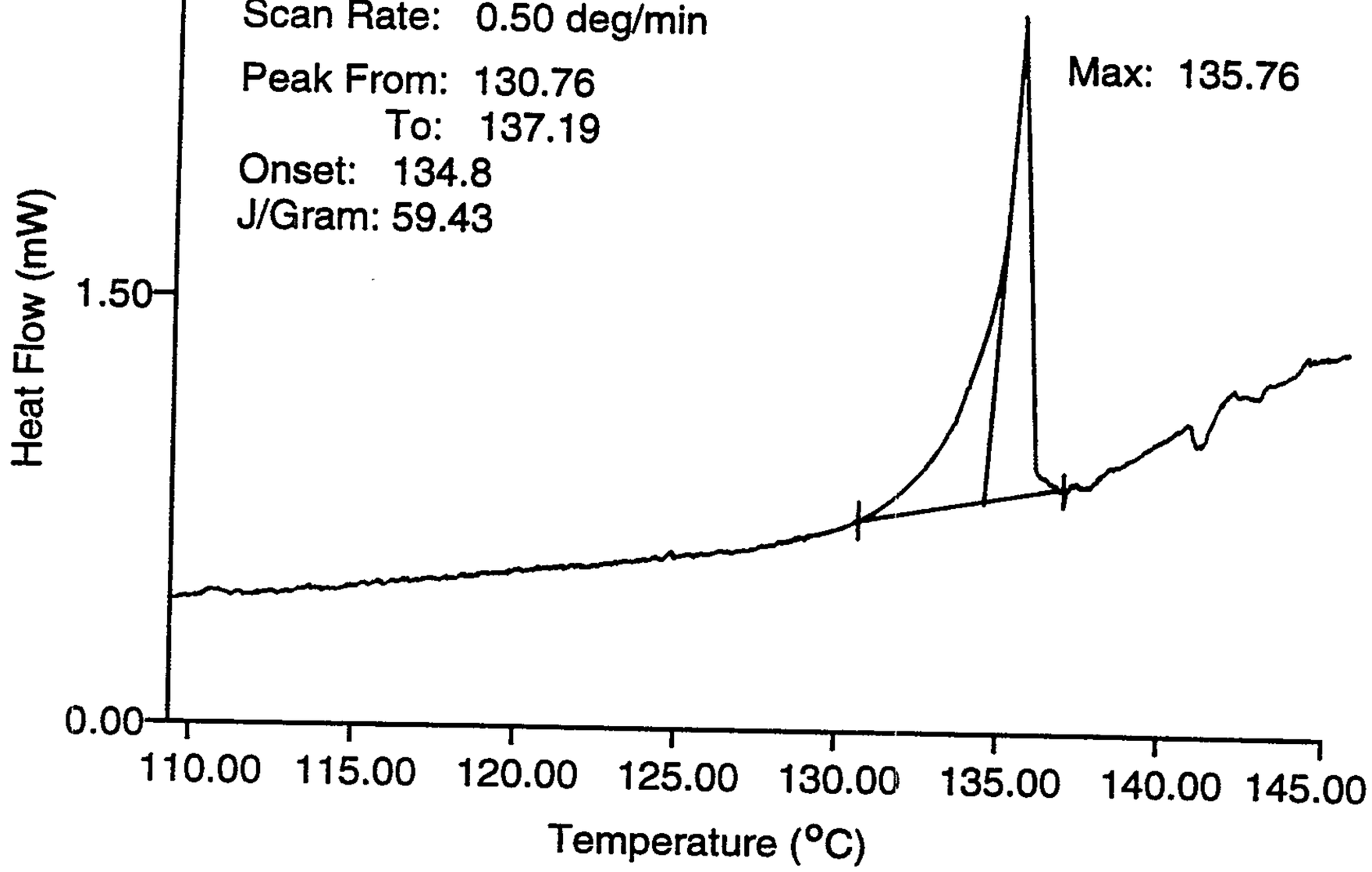

Scan Rate: 0.50 deg/min
Peak From: 130.76
To: 137.19
Onset: 134.8
J/Gram: 59.43
Max: 135.76
Heat Flow (mW)
3.00
1.50
0.00
110.00 115.00 120.00 125.00 130.00 135.00 140.00 145.00
Temperature (°C)

Fig.7.

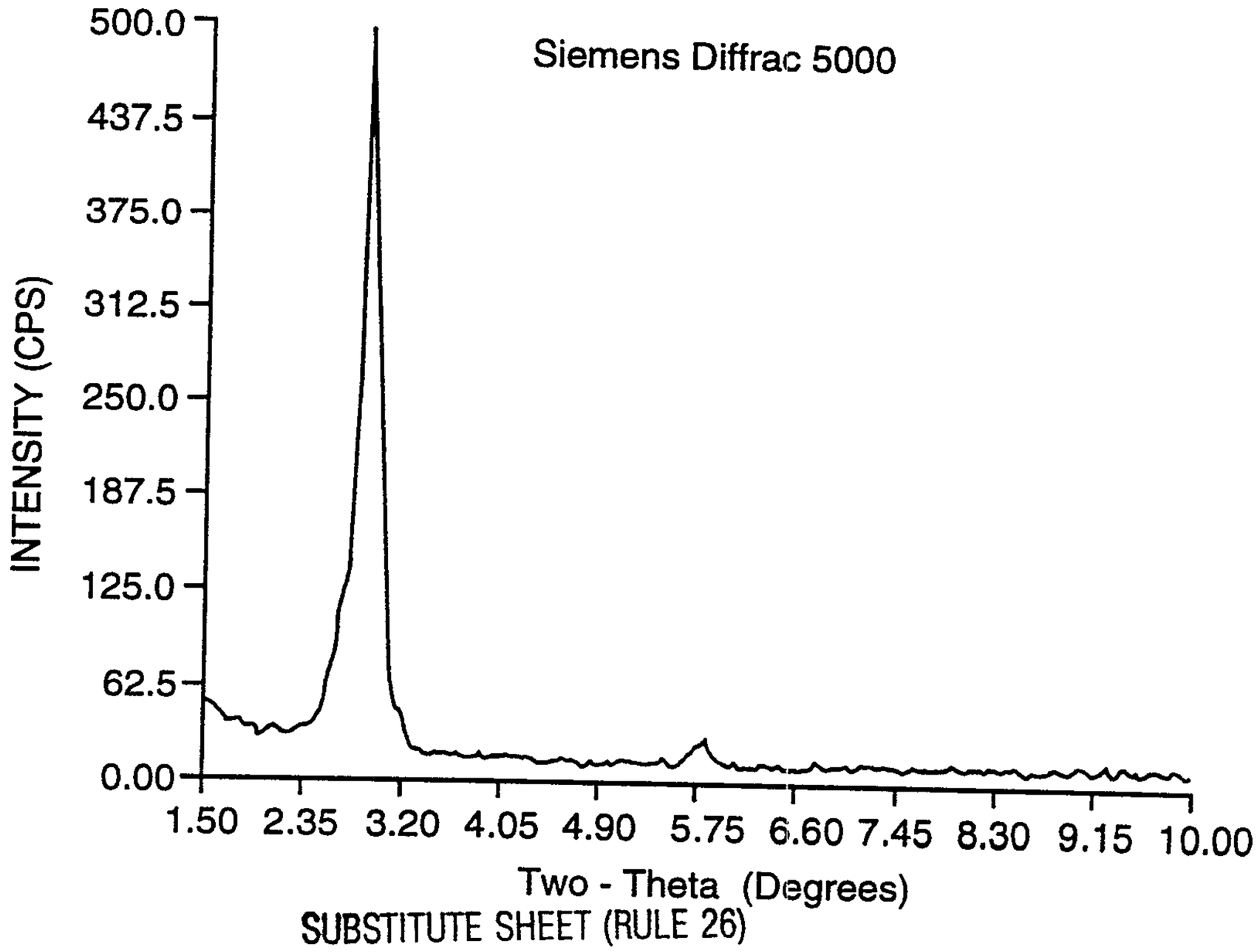

Siemens Diffrac 5000
INTENSITY (CPS)
500.0
437.5
375.0
312.5
250.0
187.5
125.0
62.5
0.00
1.50 2.35 3.20 4.05 4.90 5.75 6.60 7.45 8.30 9.15 10.00
Two - Theta (Degrees)

Fig.8.

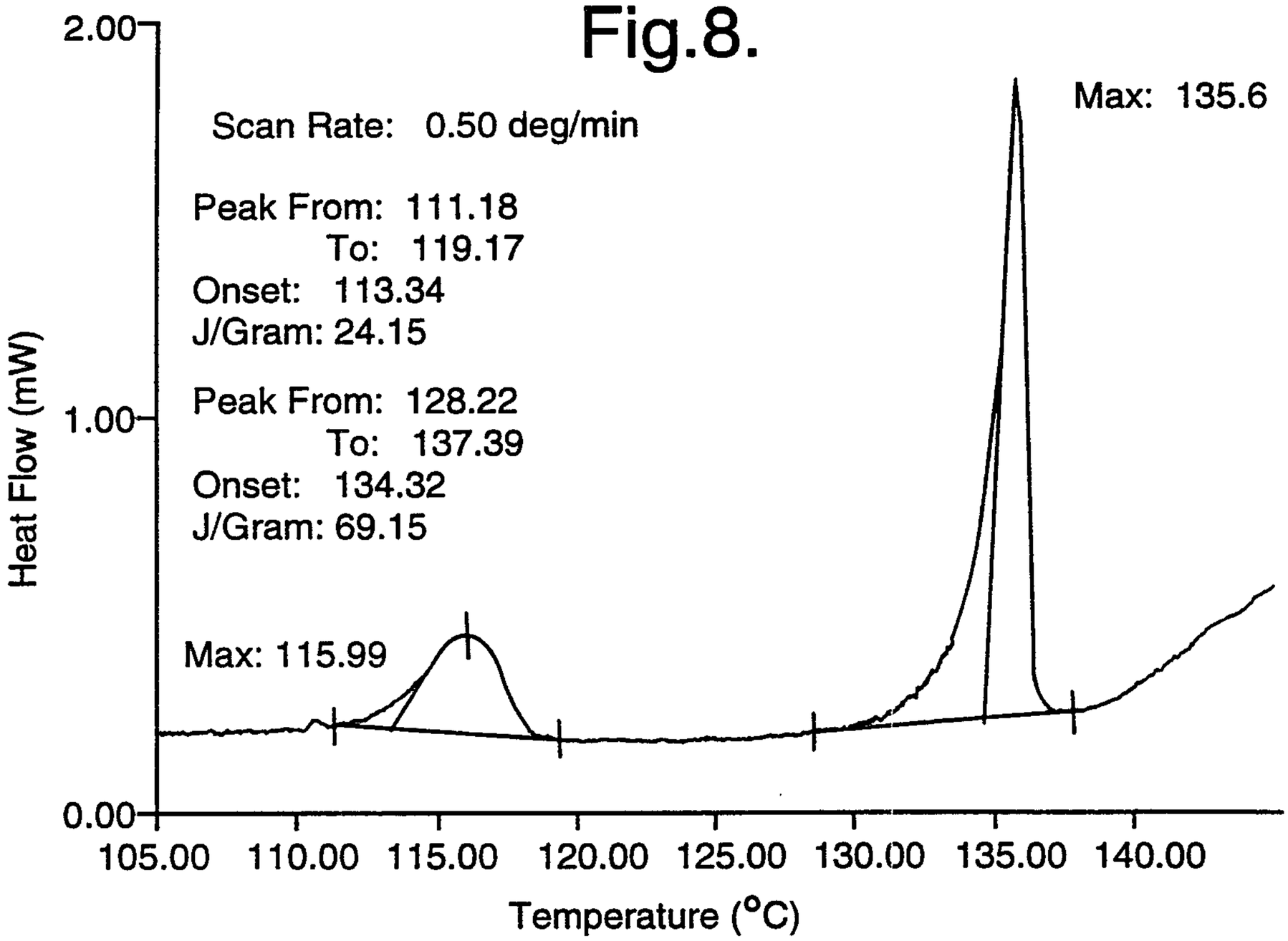
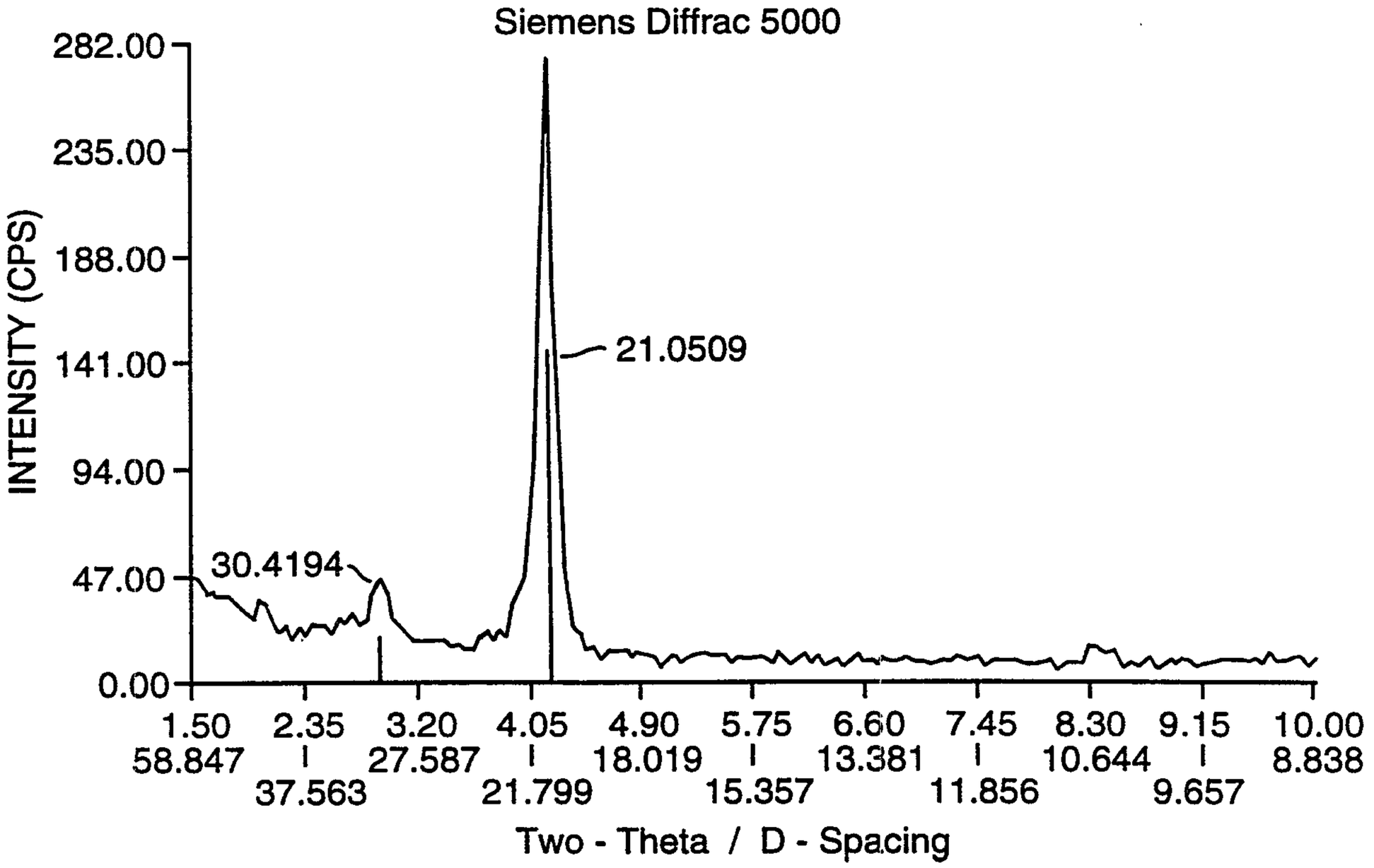

Scan Rate: 0.50 deg/min
Peak From: 111.18
To: 119.17
Onset: 113.34
J/Gram: 24.15
Peak From: 128.22
To: 137.39
Onset: 134.32
J/Gram: 69.15
Max: 115.99
Max: 135.6
Heat Flow (mW)
2.00
1.00
0.00
105.00 110.00 115.00 120.00 125.00 130.00 135.00 140.00
Temperature (°C)

Fig.9.


Siemens Diffrac 5000
INTENSITY (CPS)
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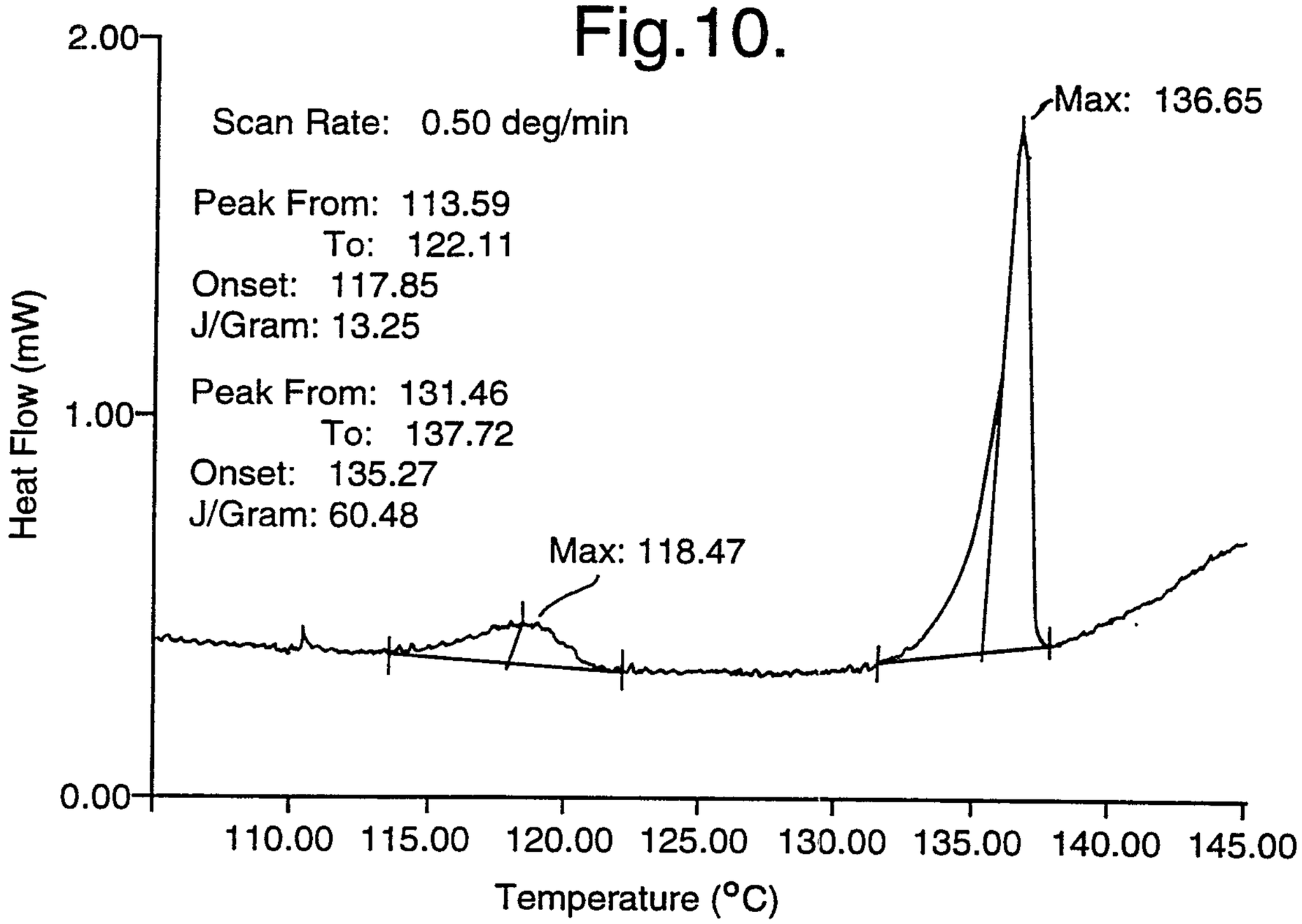
235.00
188.00
141.00
94.00
47.00
0.00
21.0509
30.4194
1.50 2.35 3.20 4.05 4.90 5.75 6.60 7.45 8.30 9.15 10.00
58.847 27.587 18.019 13.381 10.644 8.838
37.563 21.799 15.357 11.856 9.657
Two - Theta / D - Spacing

Fig.10.


Scan Rate: 0.50 deg/min
Peak From: 113.59
To: 122.11
Onset: 117.85
J/Gram: 13.25
Peak From: 131.46
To: 137.72
Onset: 135.27
J/Gram: 60.48
Max: 118.47
Max: 136.65
Heat Flow (mW)
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1.00
0.00
110.00 115.00 120.00 125.00 130.00 135.00 140.00 145.00
Temperature (°C)

Fig.11.

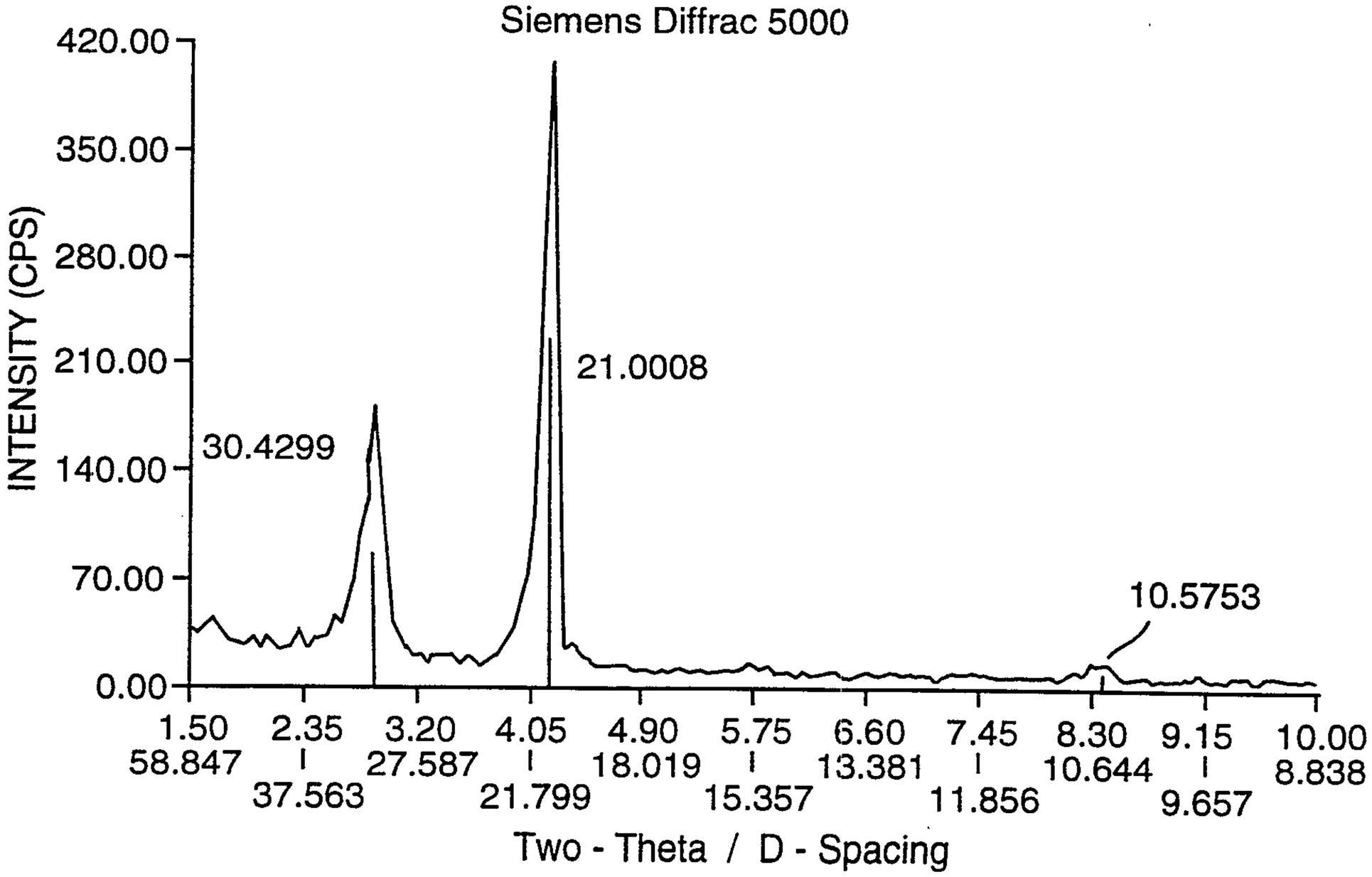

Siemens Diffrac 5000
INTENSITY (CPS)
420.00
350.00
280.00
210.00
140.00
70.00
0.00
30.4299
21.0008
10.5753
1.50 2.35 3.20 4.05 4.90 5.75 6.60 7.45 8.30 9.15 10.00
58.847 27.587 18.019 13.381 10.644 8.838
37.563 21.799 15.357 11.856 9.657
Two - Theta / D - Spacing

Fig.12. 8/29

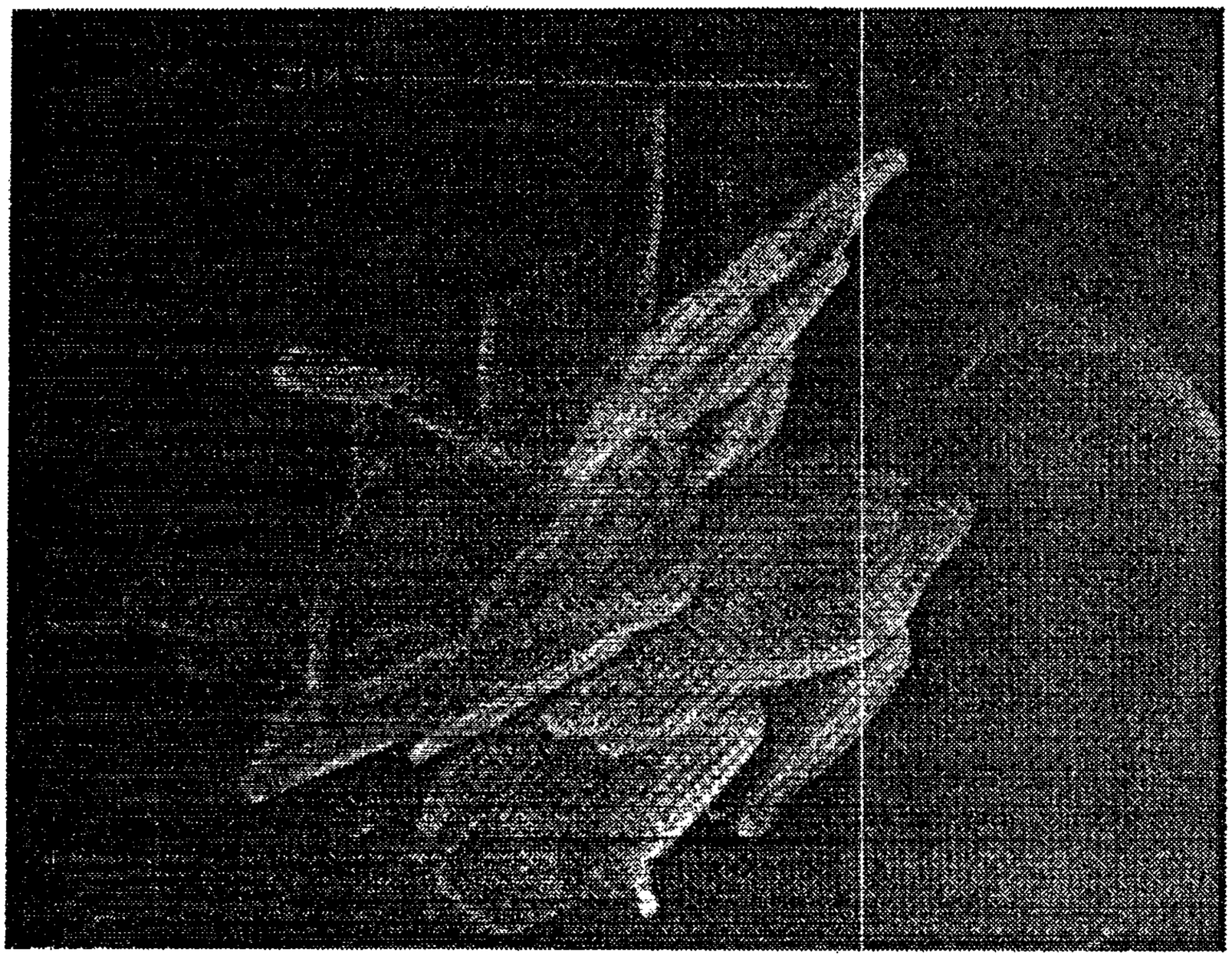


Fig.13.

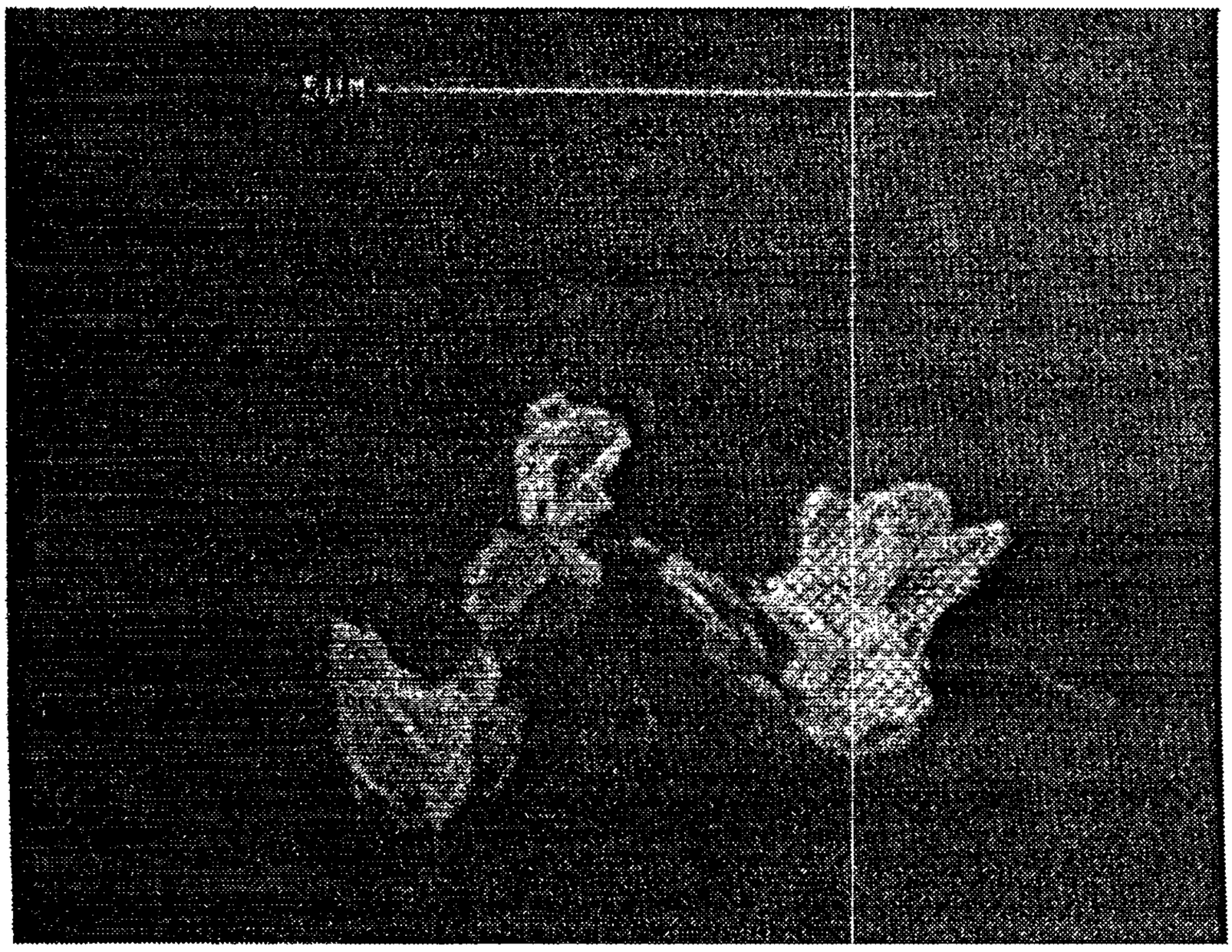


Fig.14.

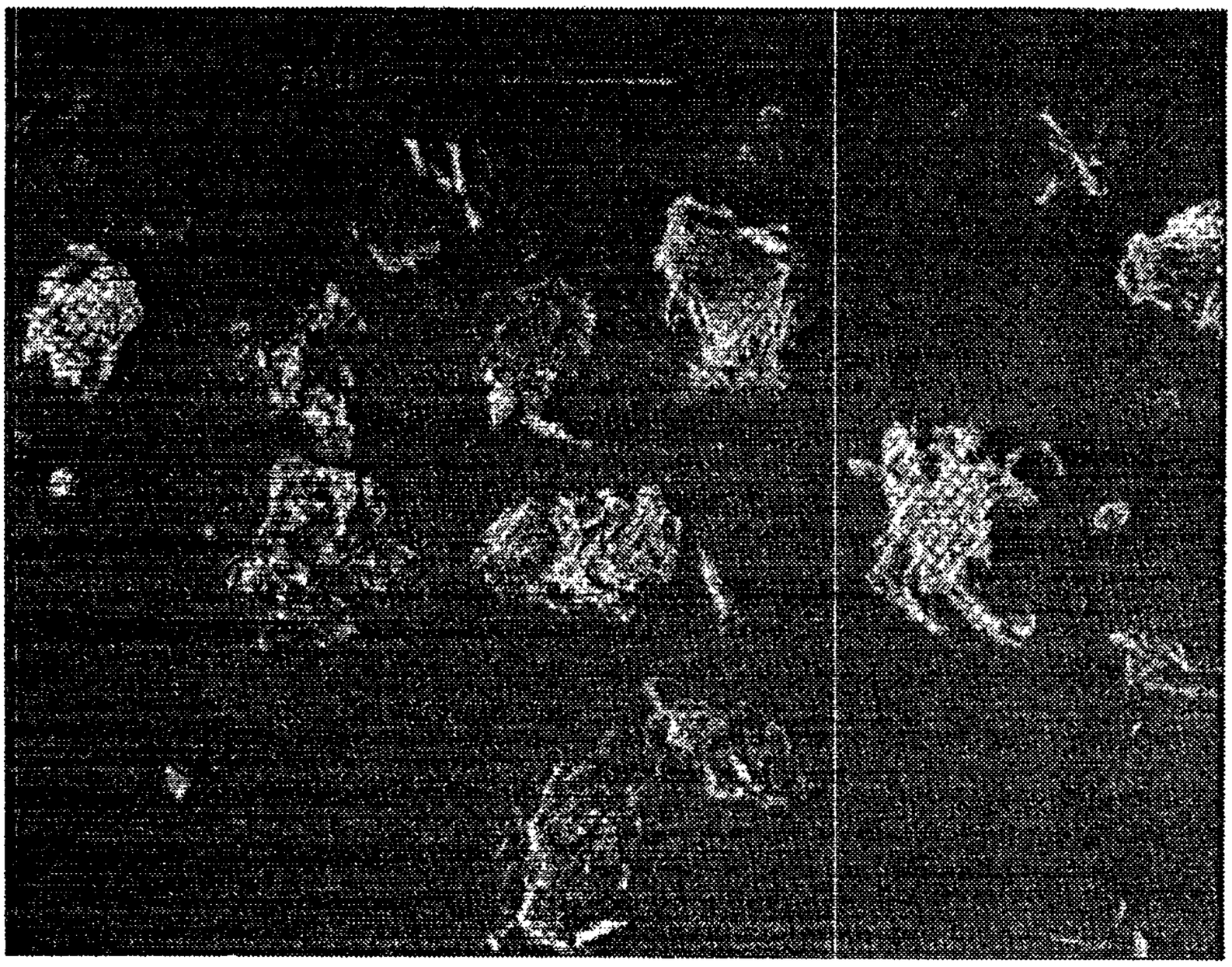


Fig.15.

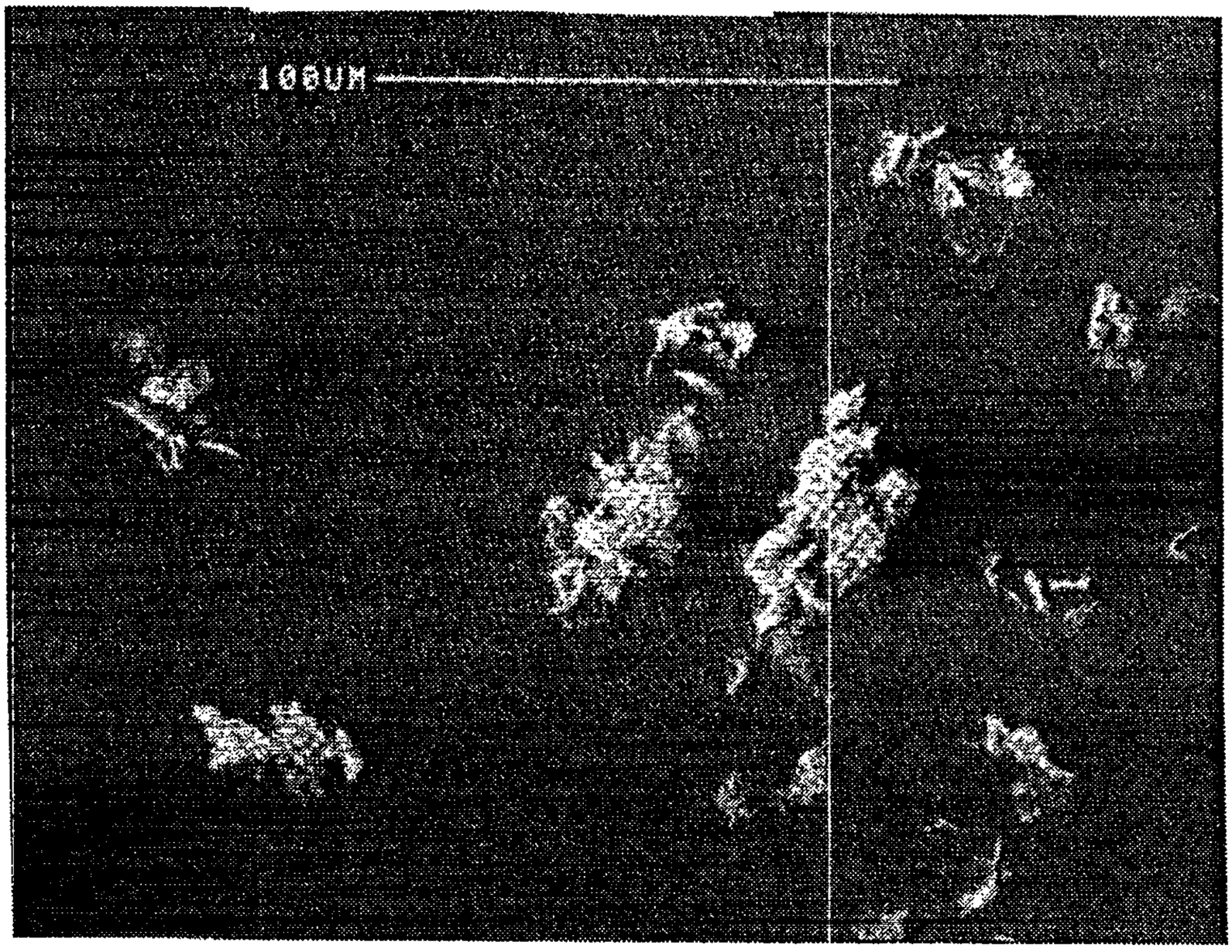


Fig.16.

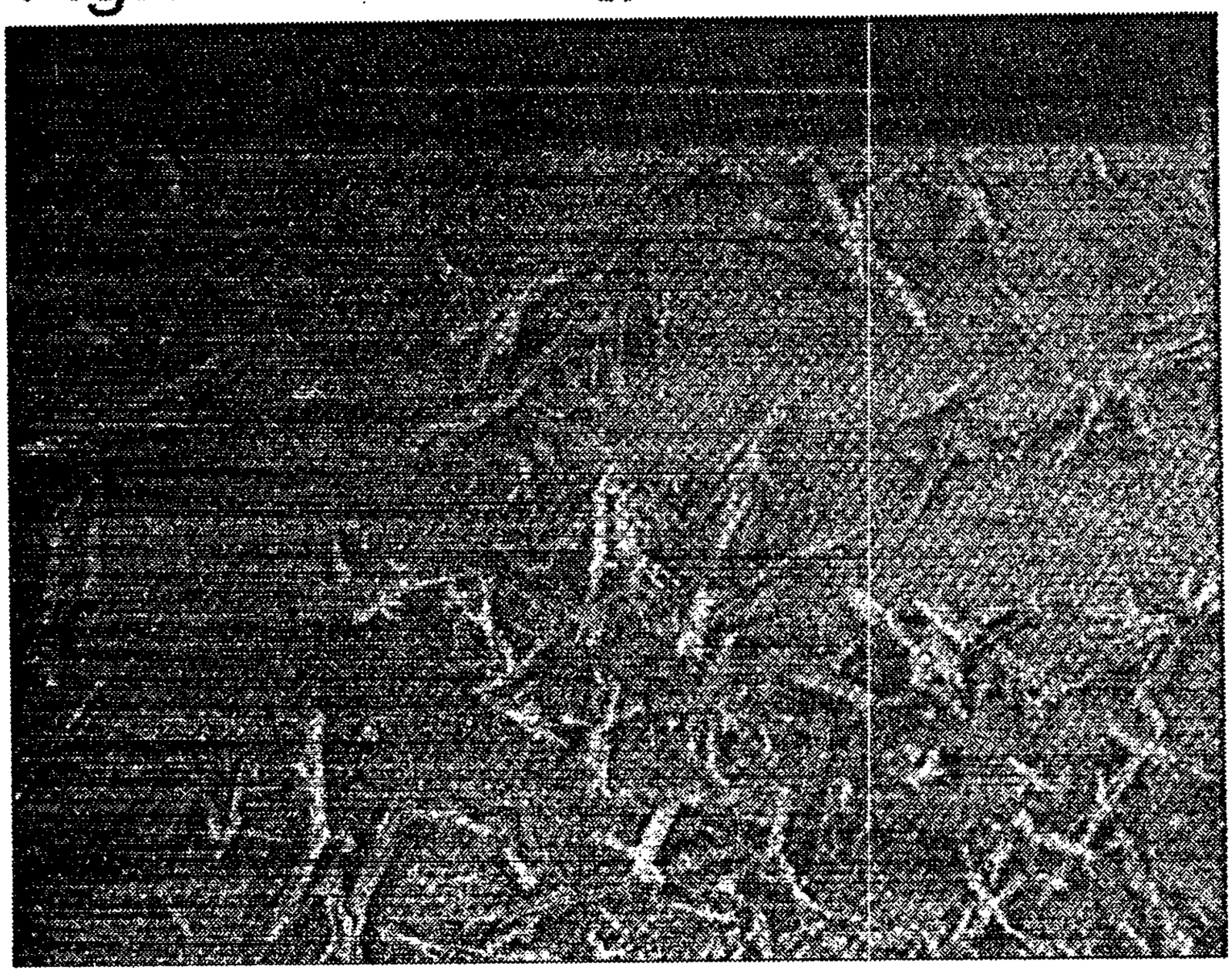


Fig.17.

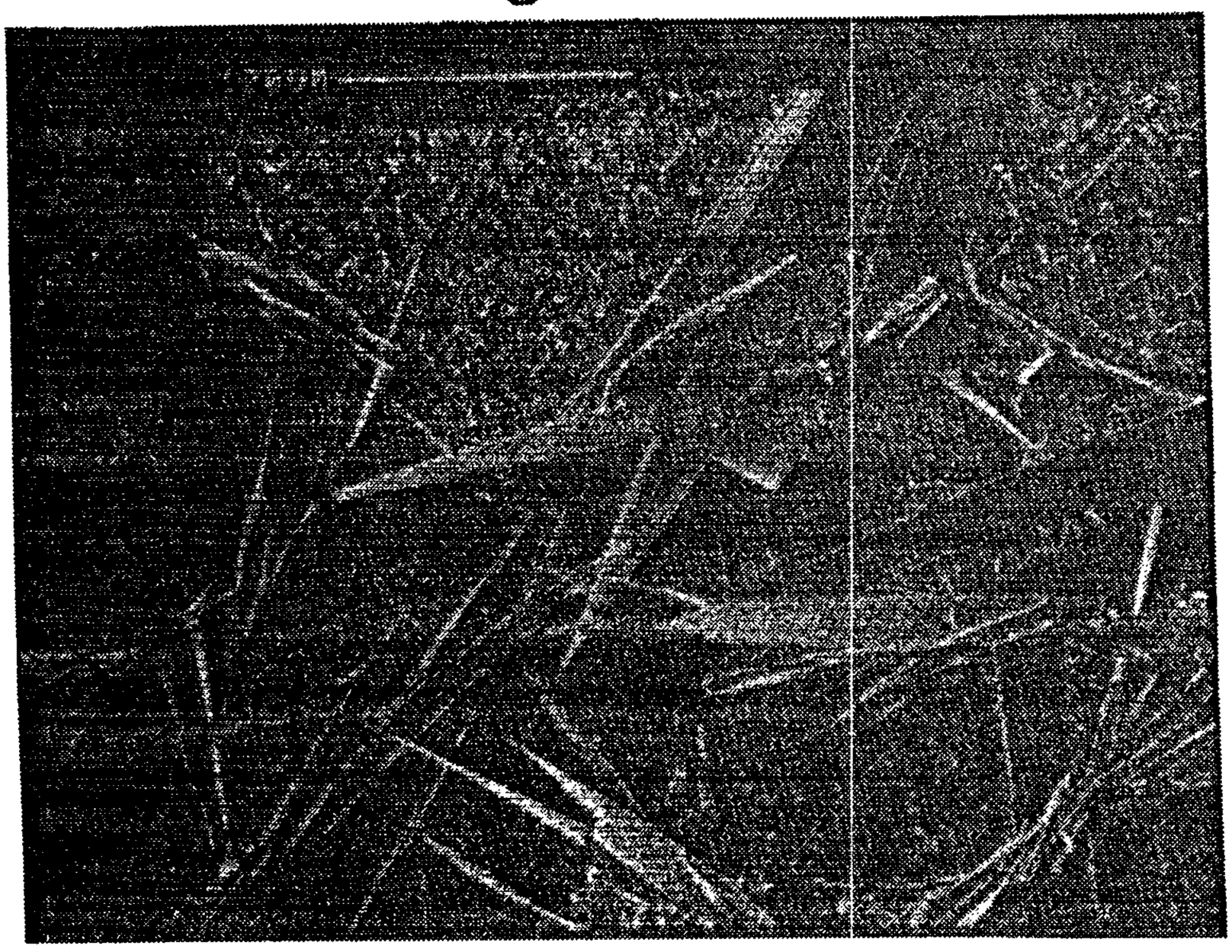


Fig.18.

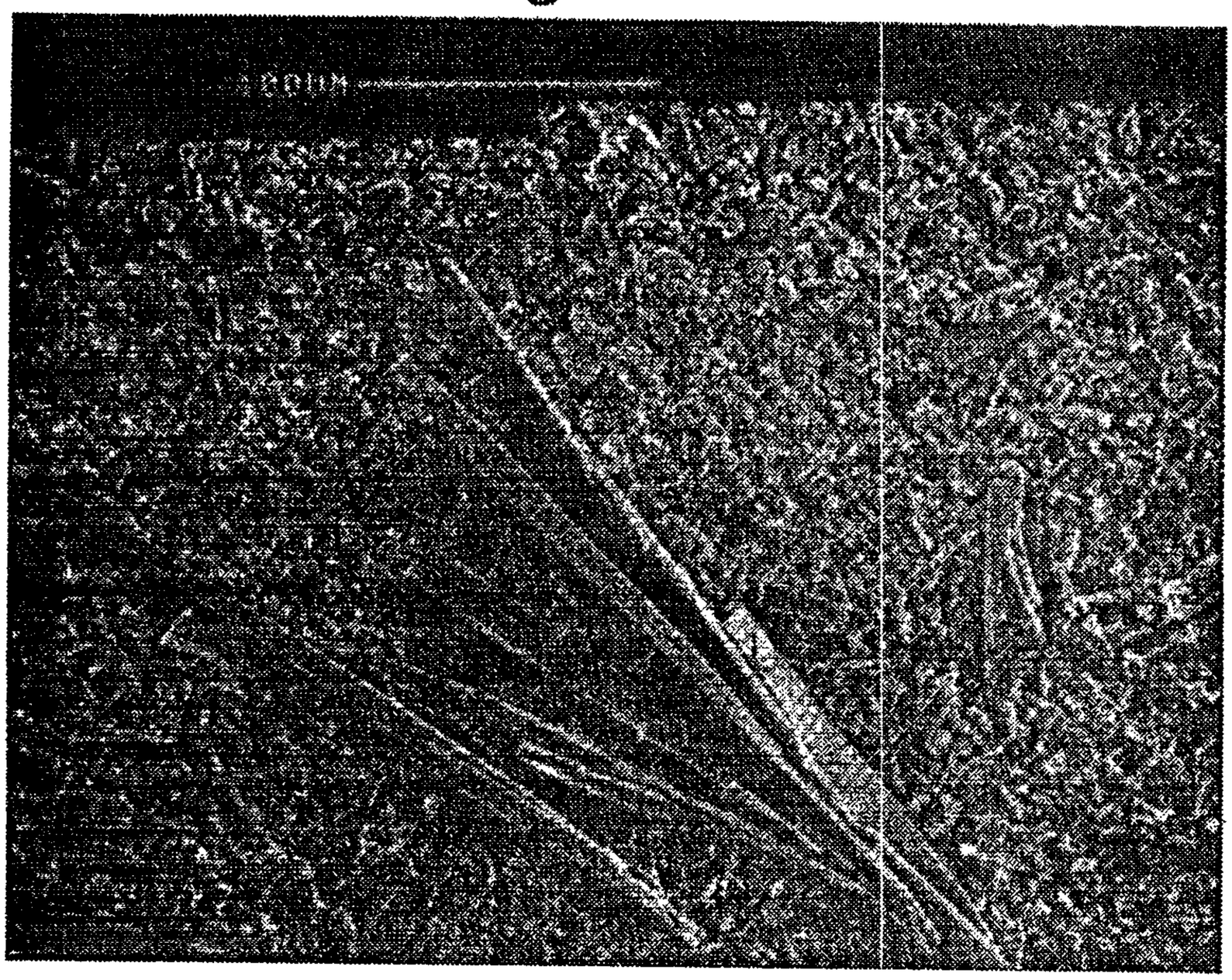


Fig.19.

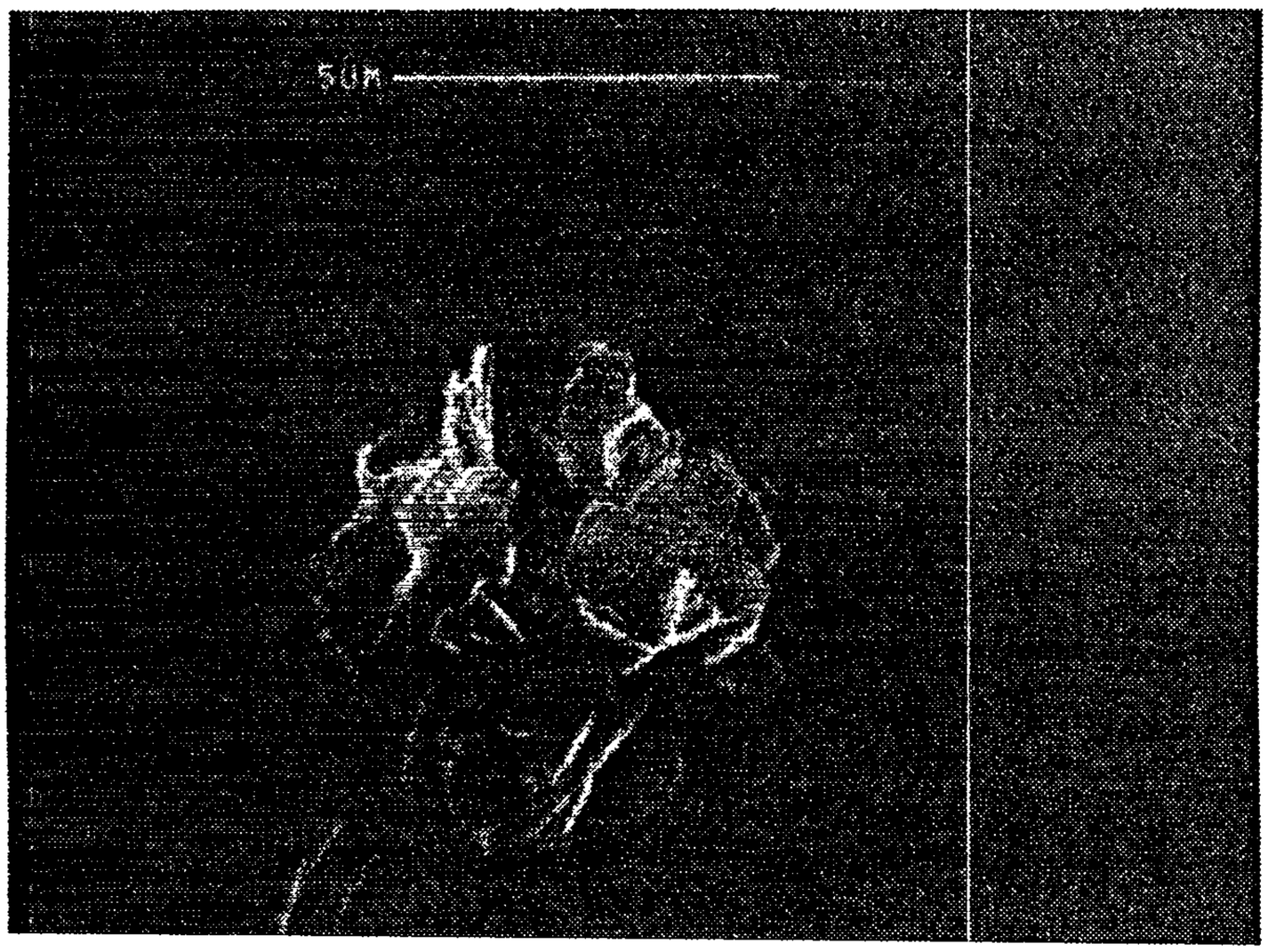


Fig.20.

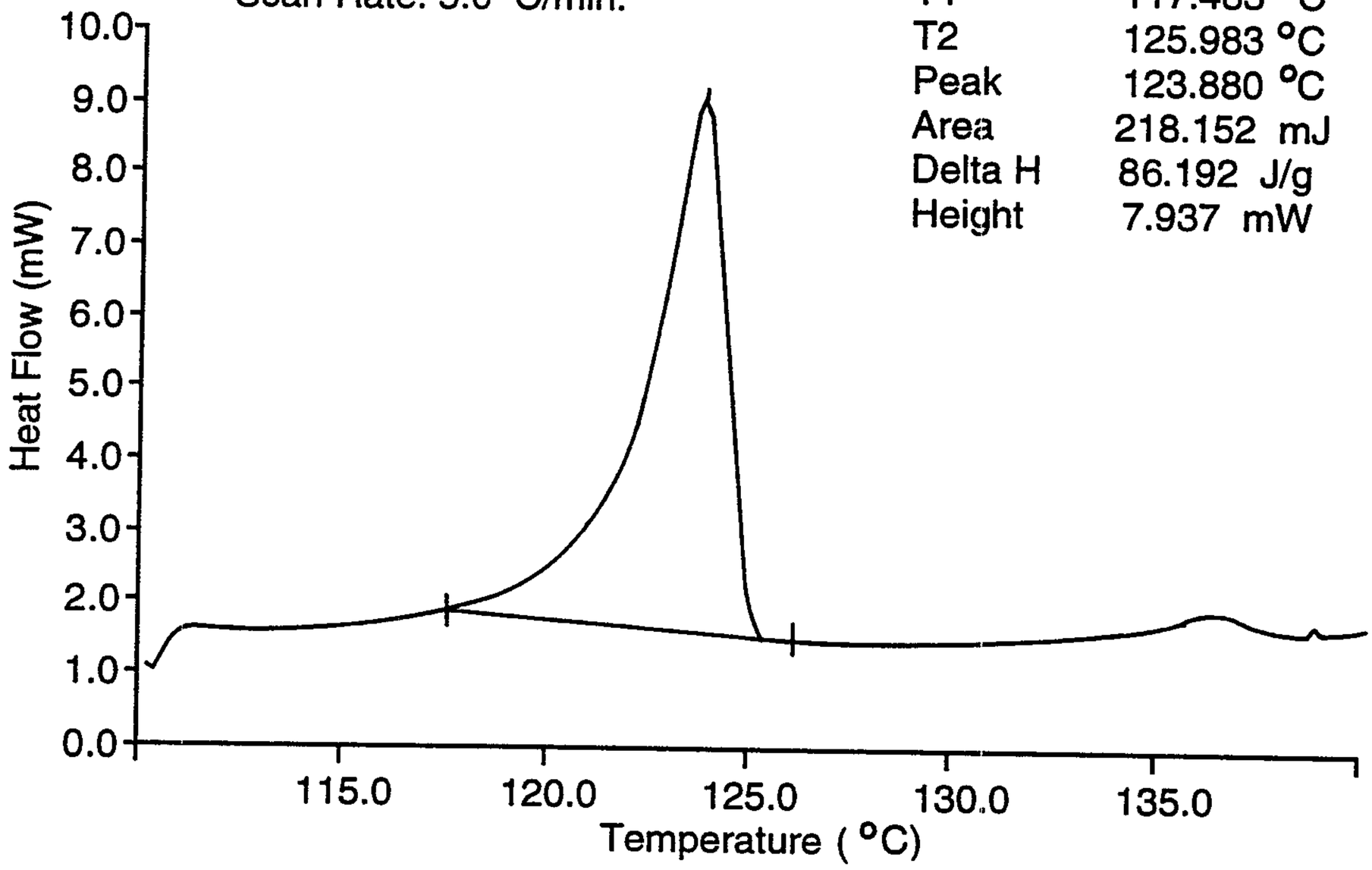

PERKIN- ELMER
7 Series Thermal Analysis System
Scan Rate: 5.0°C/min.
T1 117.483 °C
T2 125.983 °C
Peak 123.880 °C
Area 218.152 mJ
Delta H 86.192 J/g
Height 7.937 mW
Heat Flow (mW)
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
115.0
120.0
125.0
130.0
135.0
Temperature (°C)

Fig.21.

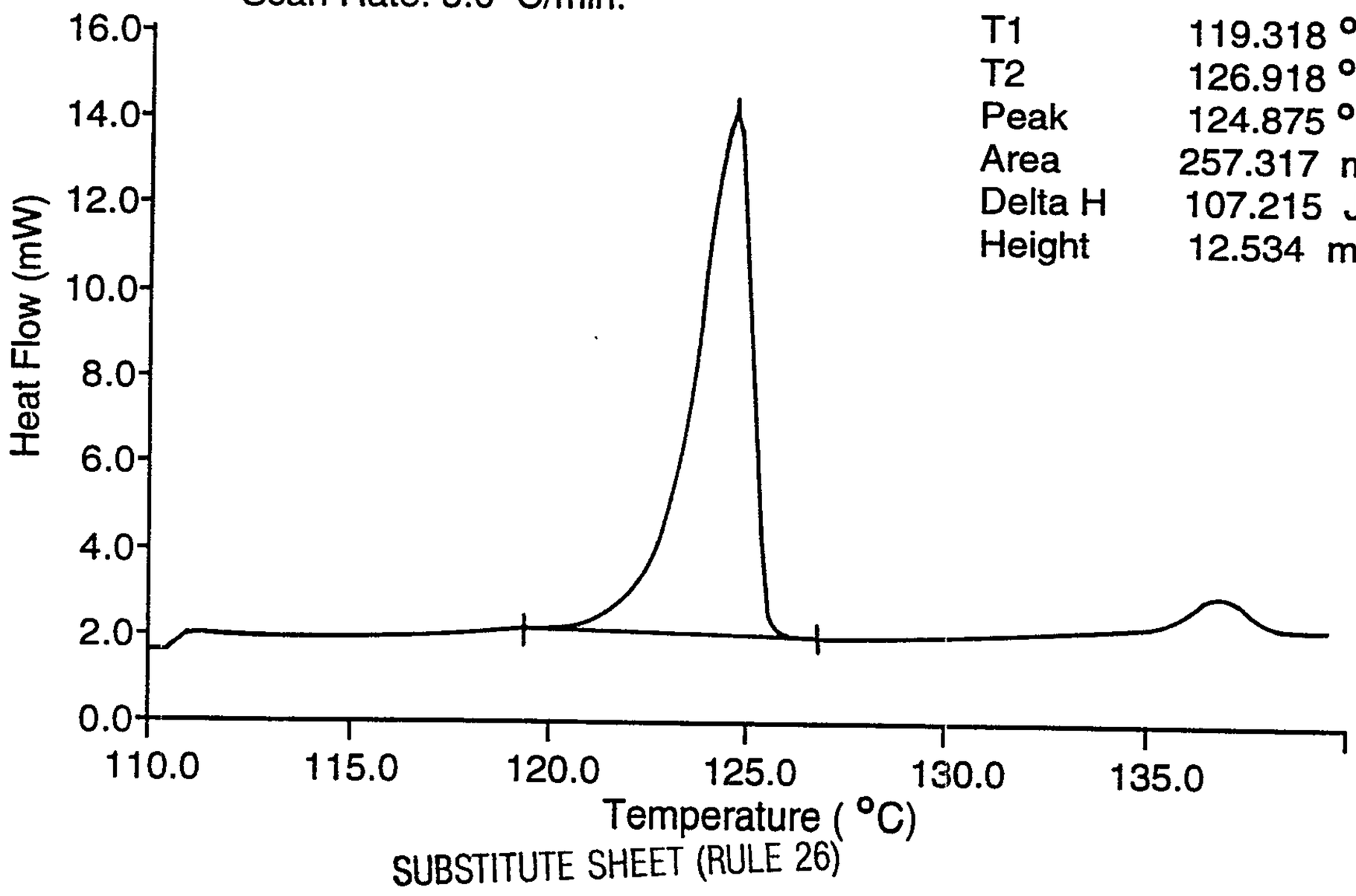

PERKIN- ELMER
7 Series Thermal Analysis System
Scan Rate: 5.0°C/min.
T1 119.318 °C
T2 126.918 °C
Peak 124.875 °C
Area 257.317 mJ
Delta H 107.215 J/g
Height 12.534 mW
Heat Flow (mW)
16.0
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
110.0
115.0
120.0
125.0
130.0
135.0
Temperature (°C)

FIG.22.

SIEMENS DIFFRAC - 5000

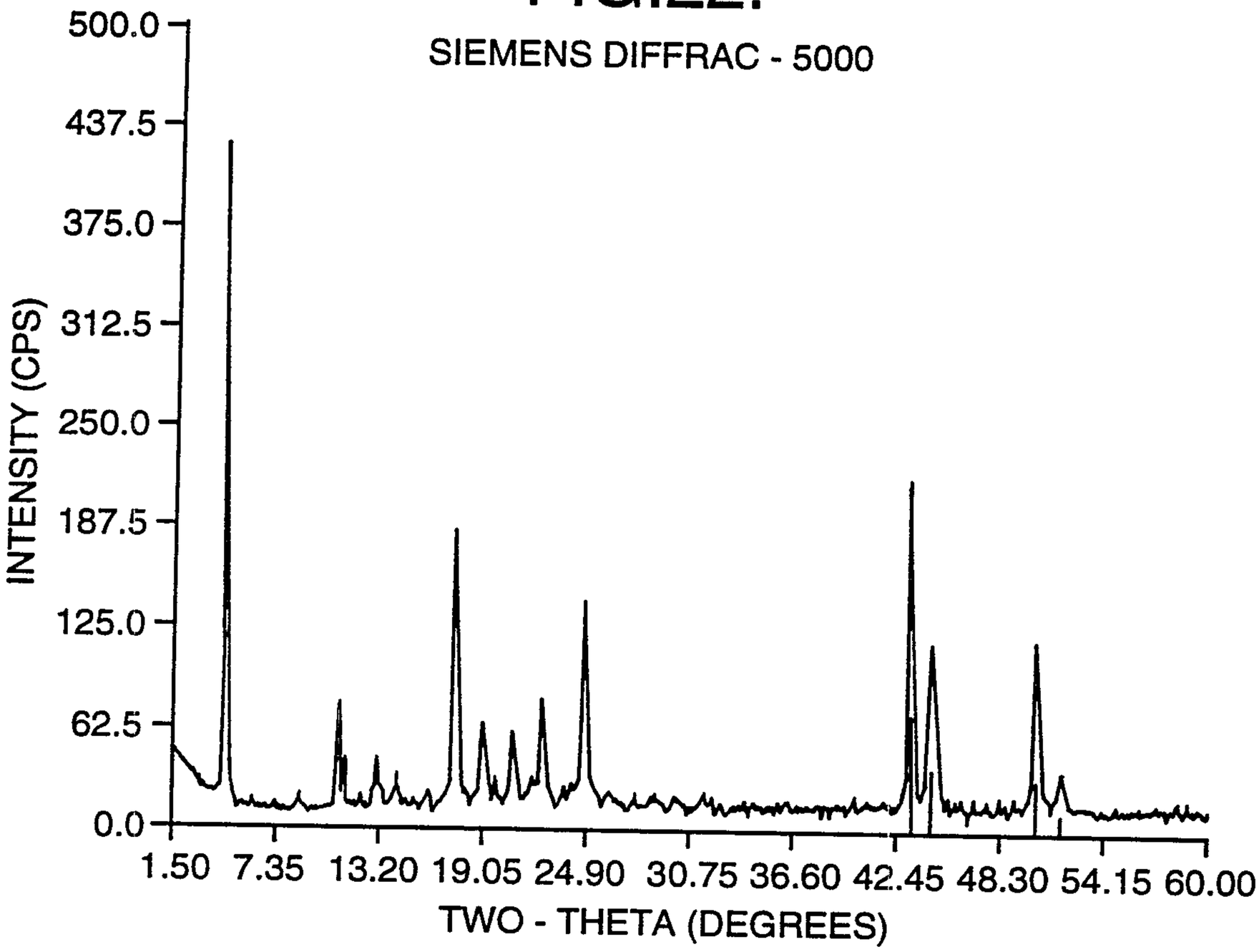


FIG.23.

SIEMENS DIFFRAC - 5000

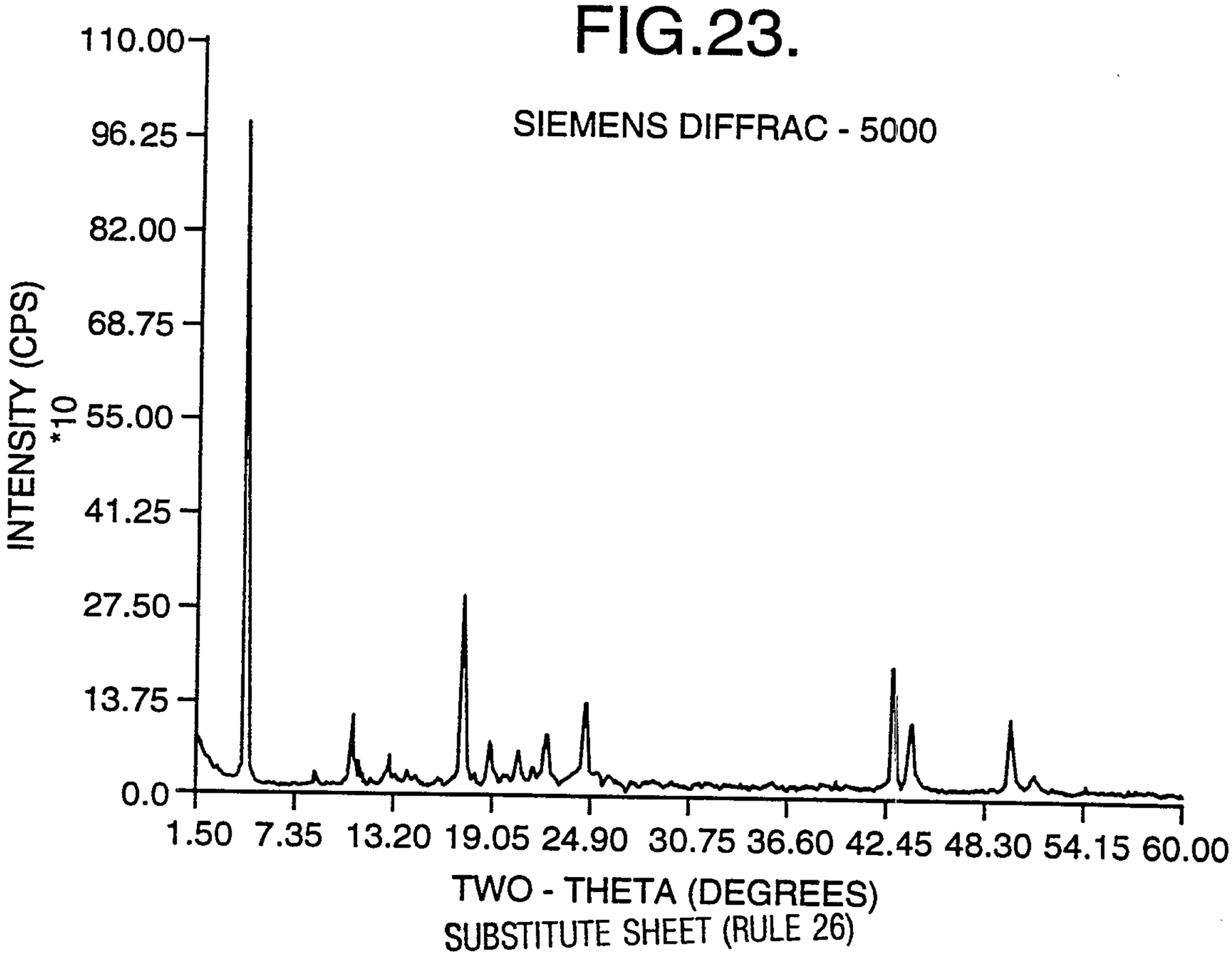


Fig.24.A

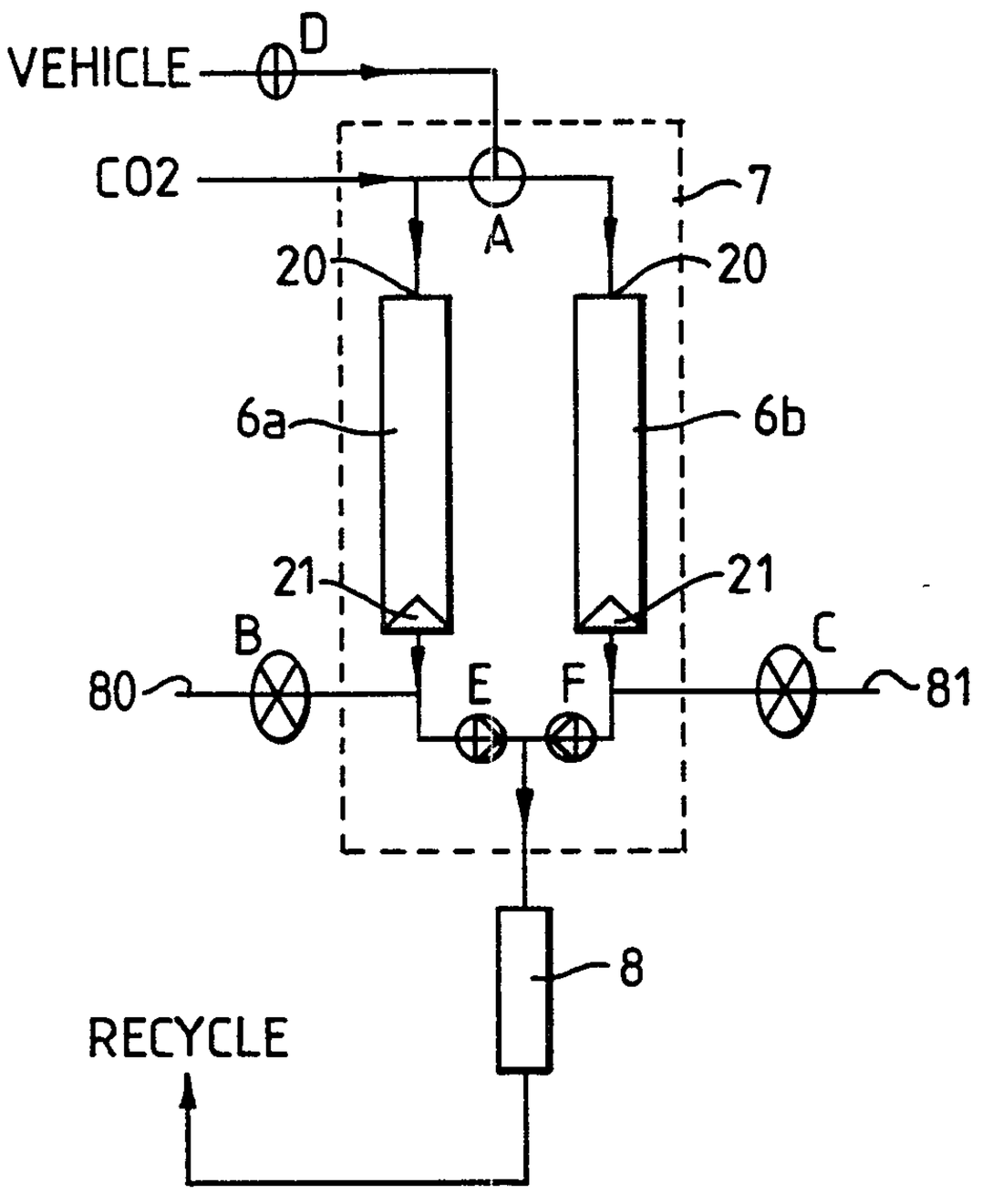


Fig.24.B

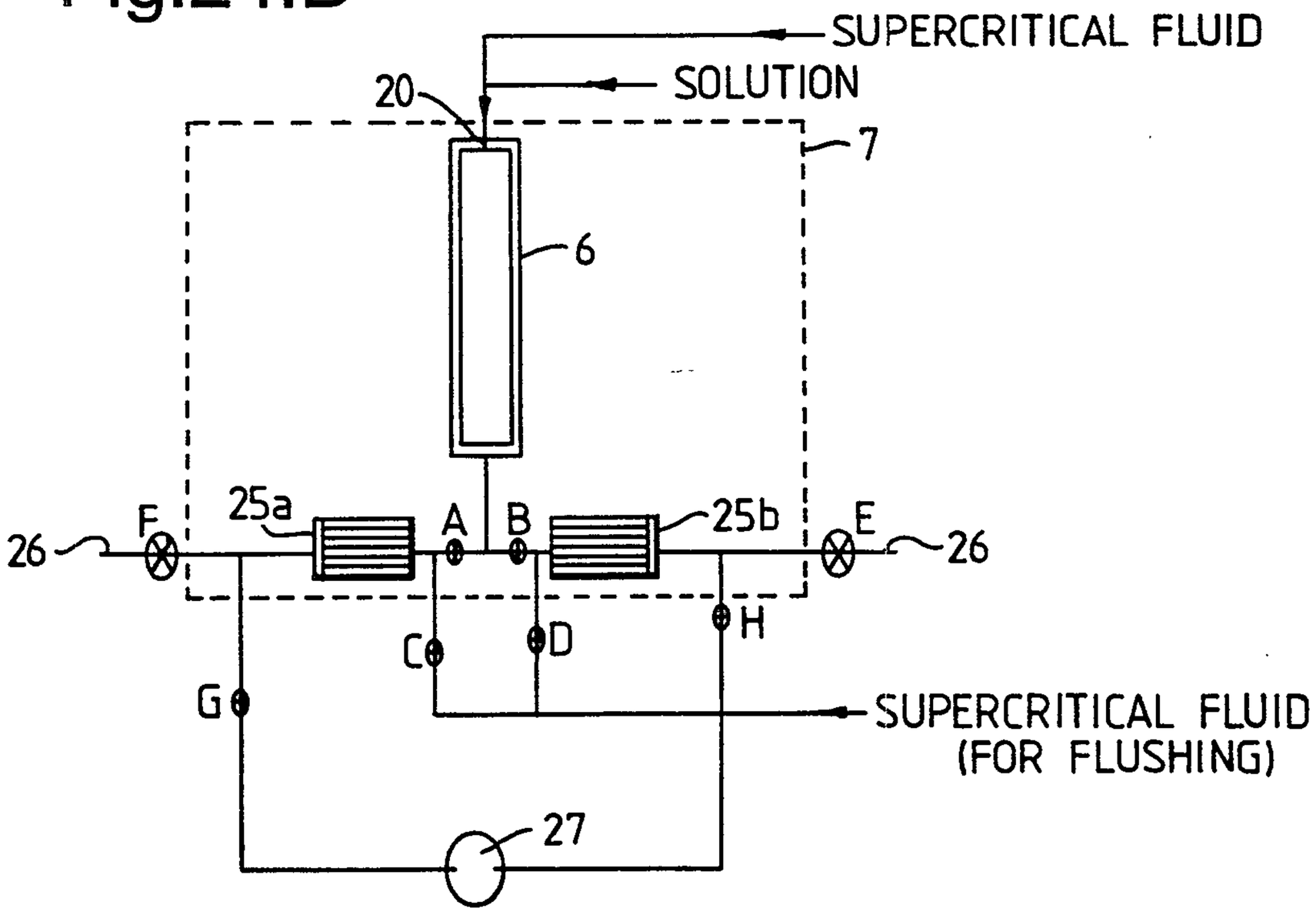


Fig.25.

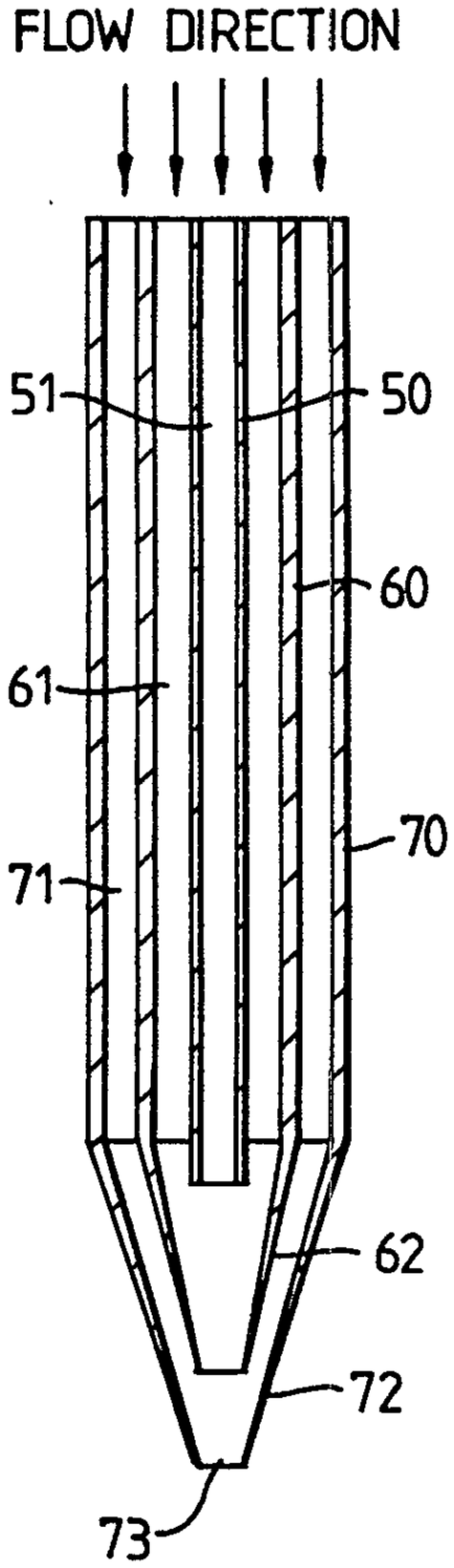


Fig.26.

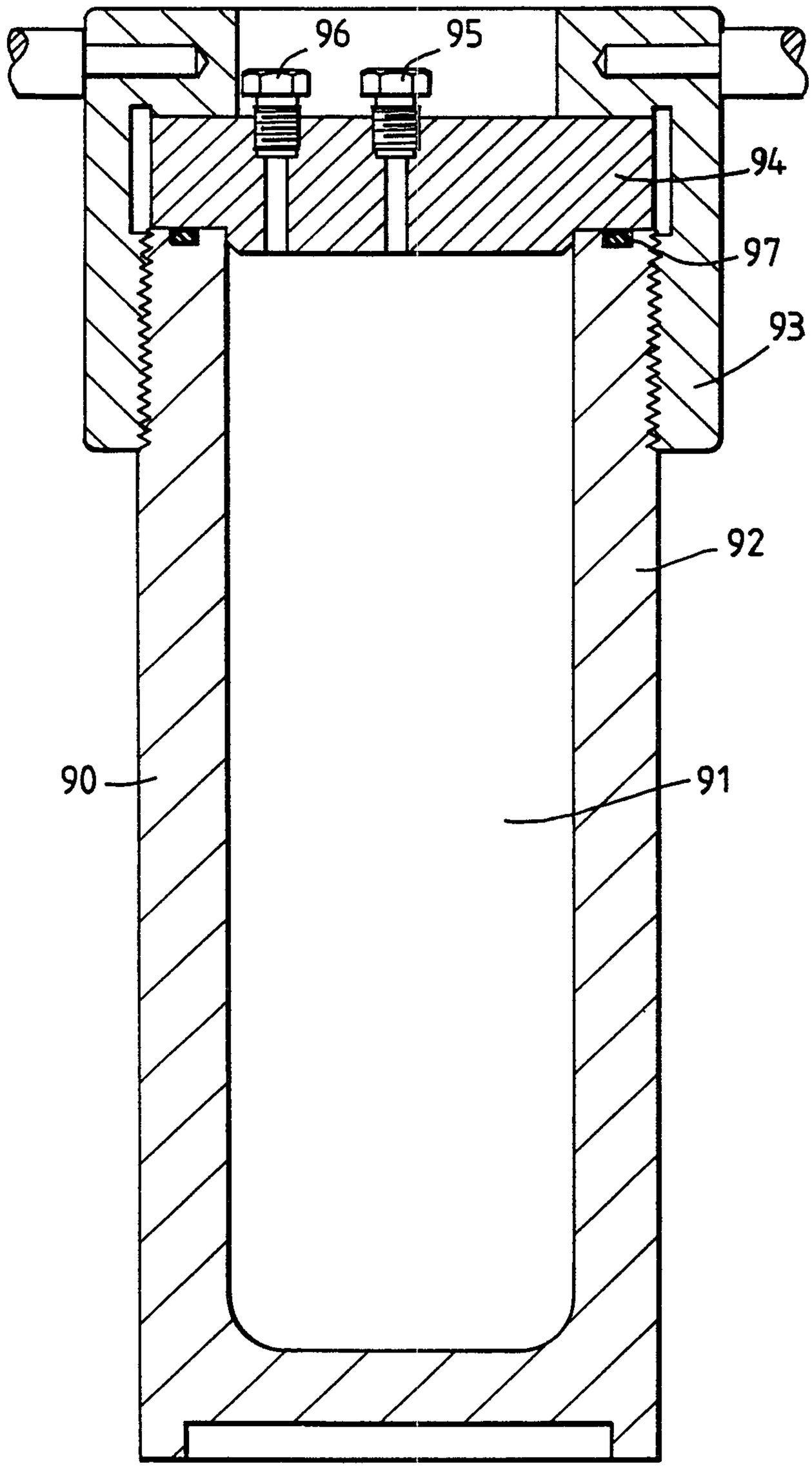


Fig.27.

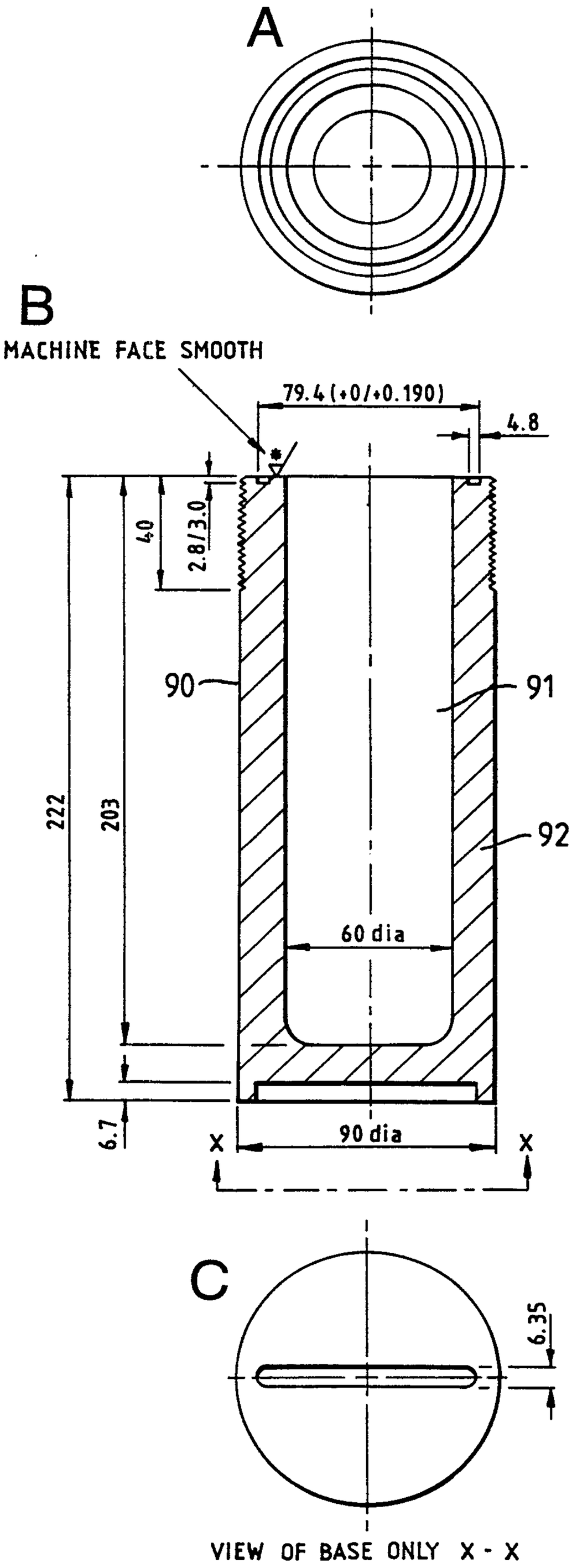

A
B
MACHINE FACE SMOOTH
79.4 (+0/+0.190)
4.8
40
2.8/3.0
90
91
92
222
203
6.7
60 dia
90 dia
X
X
C
6.35
VIEW OF BASE ONLY X - X
D
DRILL 2 DIAMETRICALLY OPPOSITE HOLES 6mm DIA. 20mm DEEP FOR 2 130mm LONG HANDLES
110
94
86
55
18
10
20
79
38
8
93
REMOVE SHARP CORNERS
E
86
24
22
20
94
45°
SLIDING FIT
MACHINE FACE SMOOHT
F
72.62 ± 0.61
3.53 ± 0.10
97
Scale :
0
50

Fig.28.

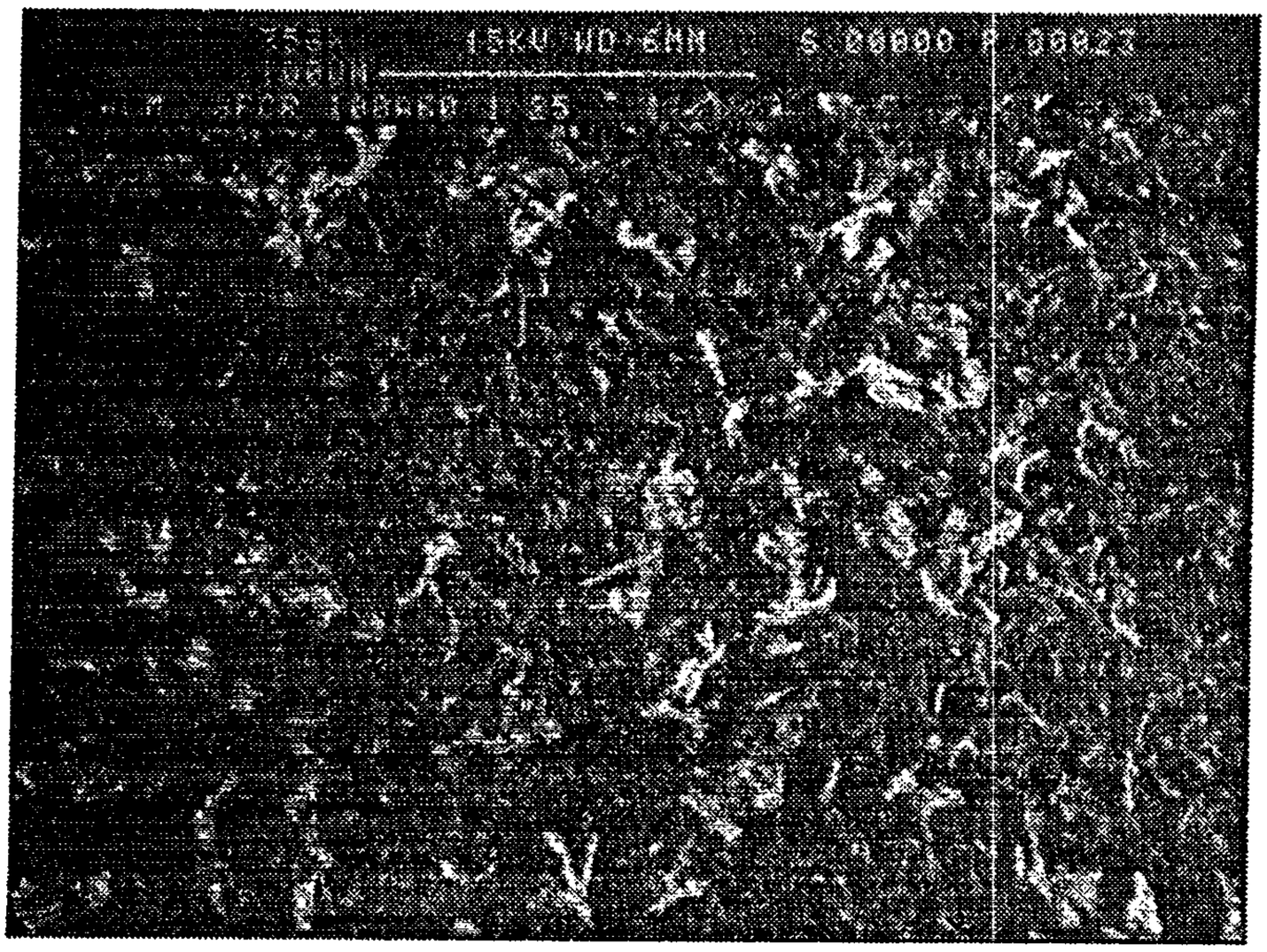


Fig.29.

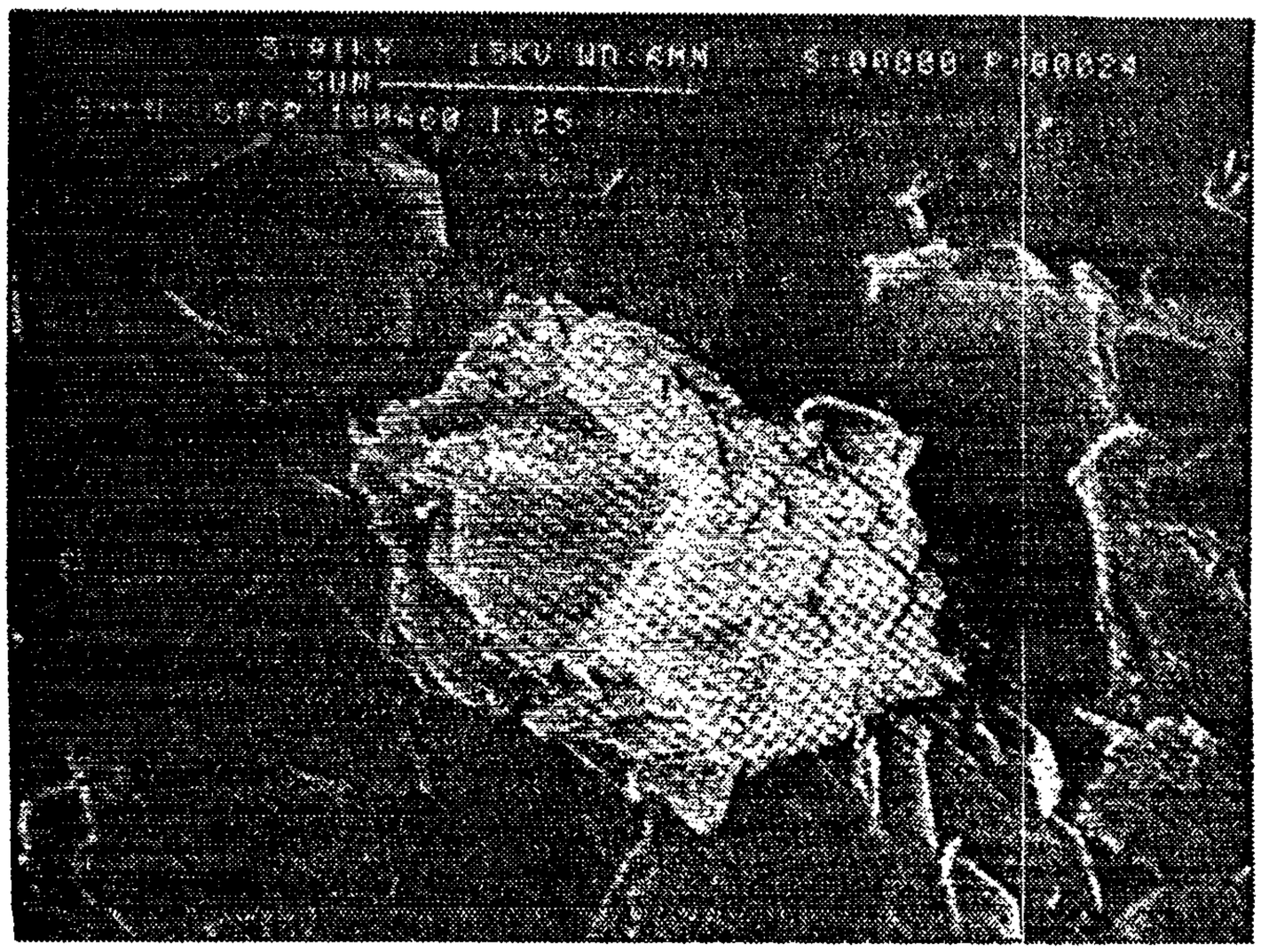


FIG.30.

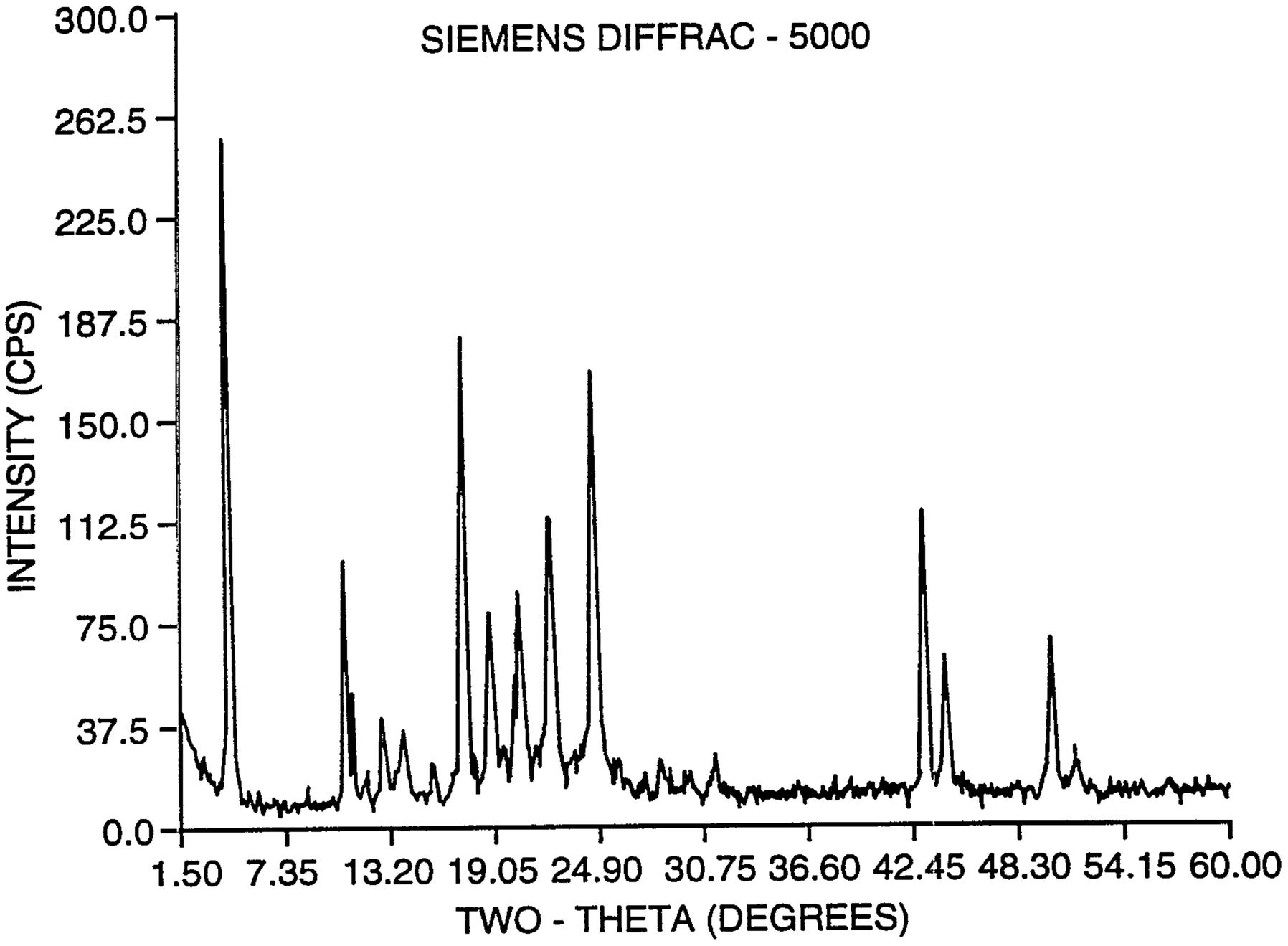

SIEMENS DIFFRAC - 5000
INTENSITY (CPS)
300.0
262.5
225.0
187.5
150.0
112.5
75.0
37.5
0.0
1.50 7.35 13.20 19.05 24.90 30.75 36.60 42.45 48.30 54.15 60.00
TWO - THETA (DEGREES)

FIG.31.

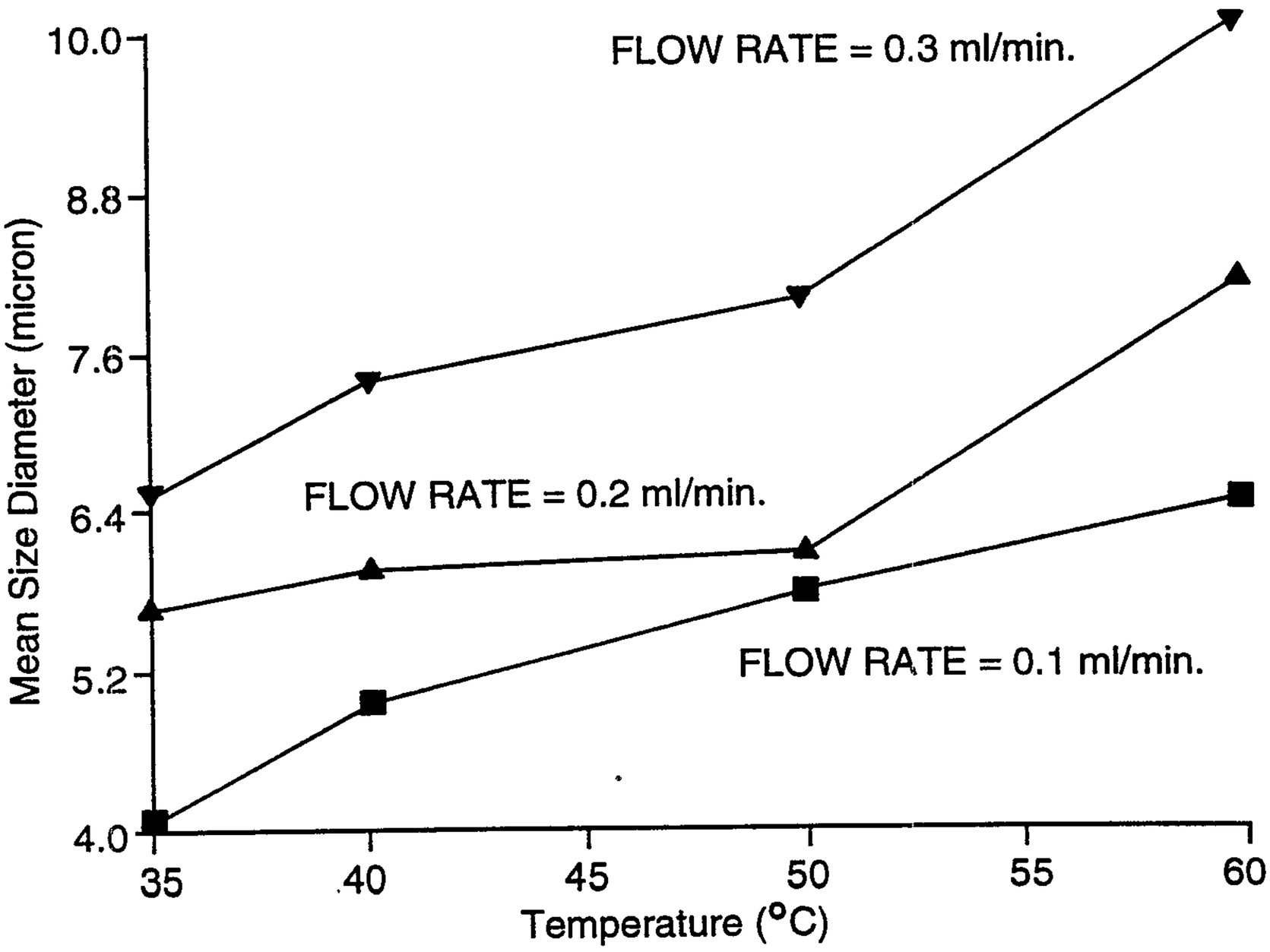

FLOW RATE = 0.3 ml/min.
FLOW RATE = 0.2 ml/min.
FLOW RATE = 0.1 ml/min.
Mean Size Diameter (micron)
10.0
8.8
7.6
6.4
5.2
4.0
35
40
45
50
55
60
Temperature (°C)

FIG.32.

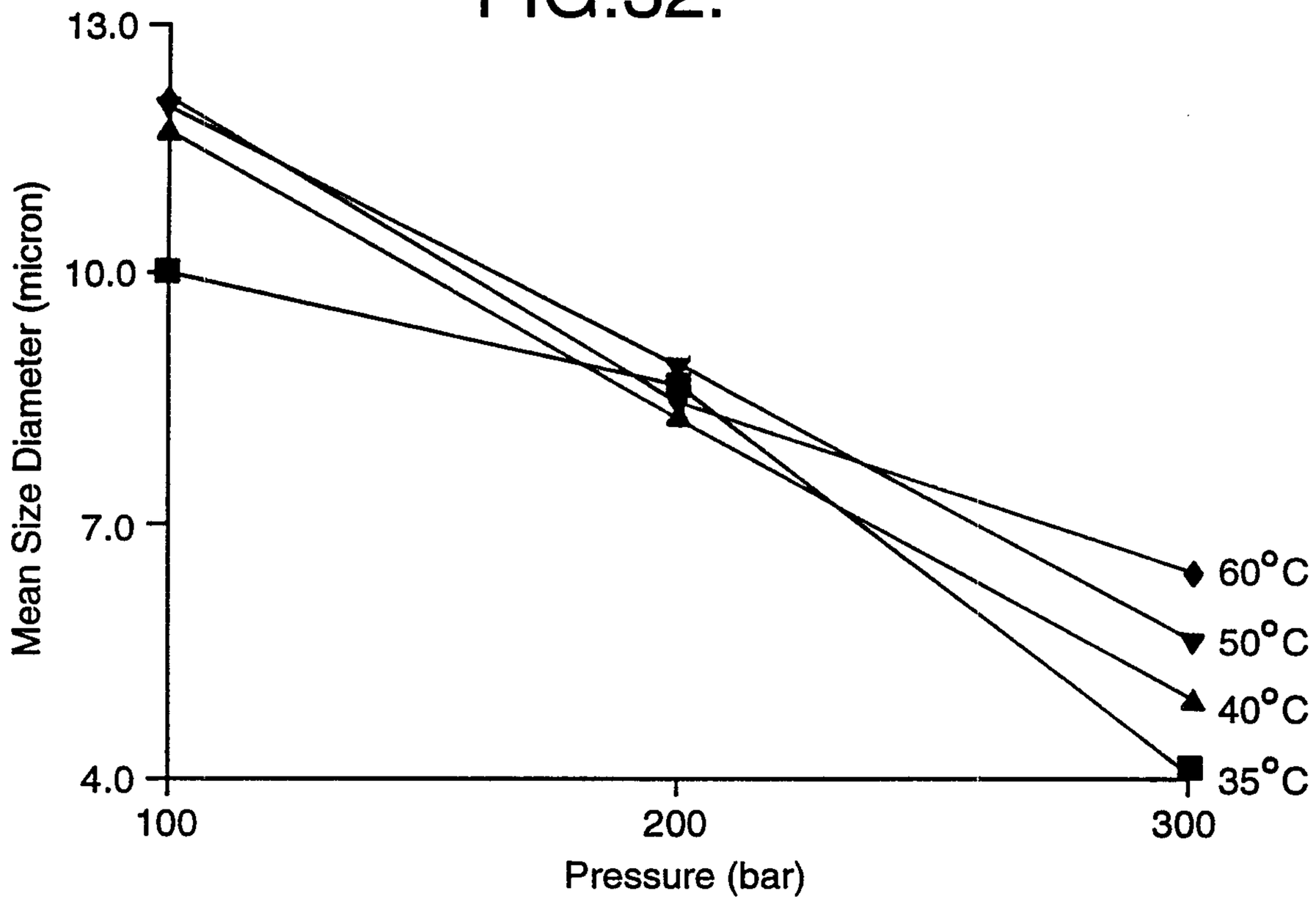

13.0
10.0
7.0
4.0
Mean Size Diameter (micron)
100
200
300
Pressure (bar)
60°C
50°C
40°C
35°C

FIG.33.

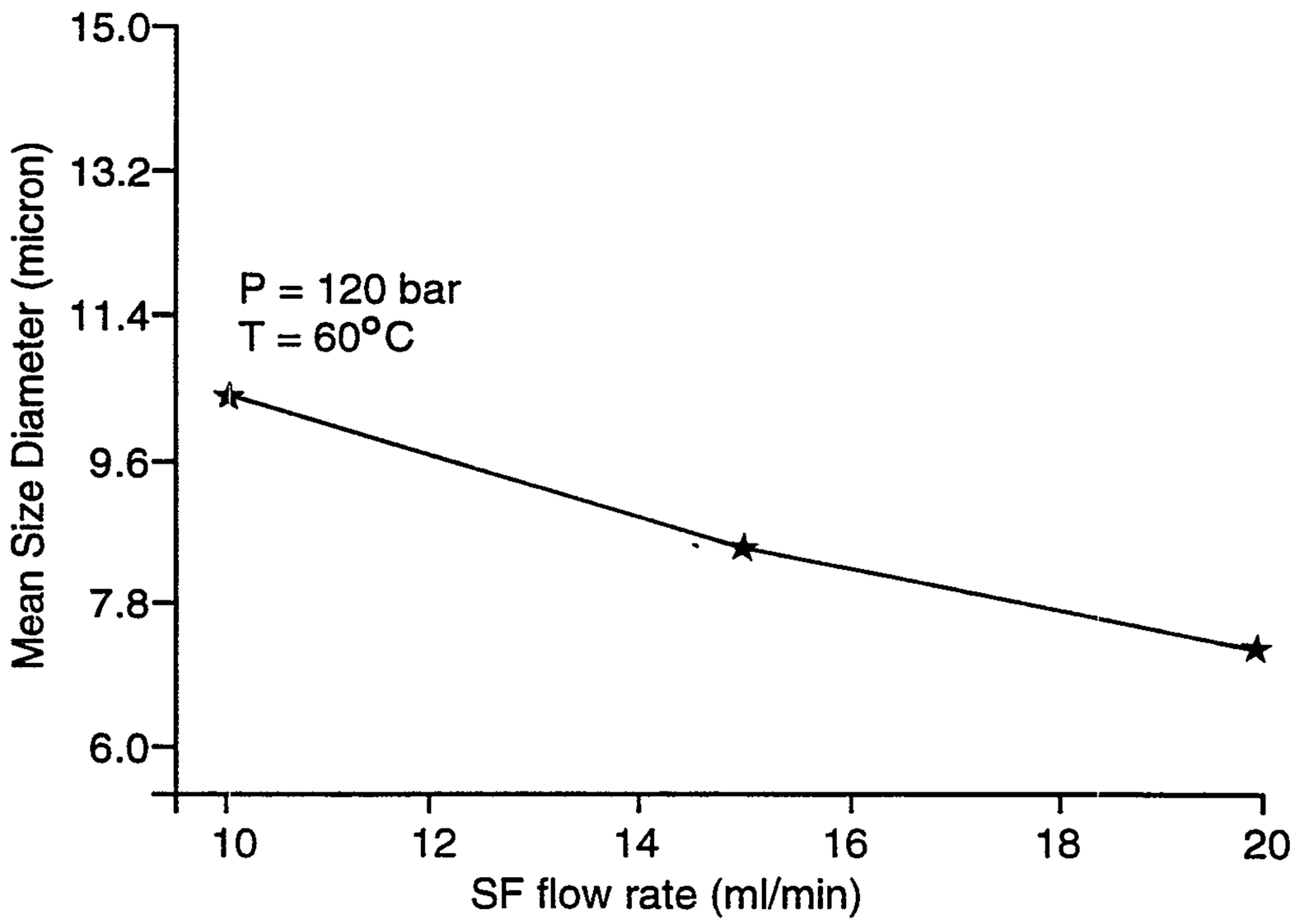

15.0
13.2
11.4
9.6
7.8
6.0
Mean Size Diameter (micron)
P = 120 bar
T = 60°C
10
12
14
16
18
20
SF flow rate (ml/min)

FIG.34.

SIEMENS DIFFRAC - 5000

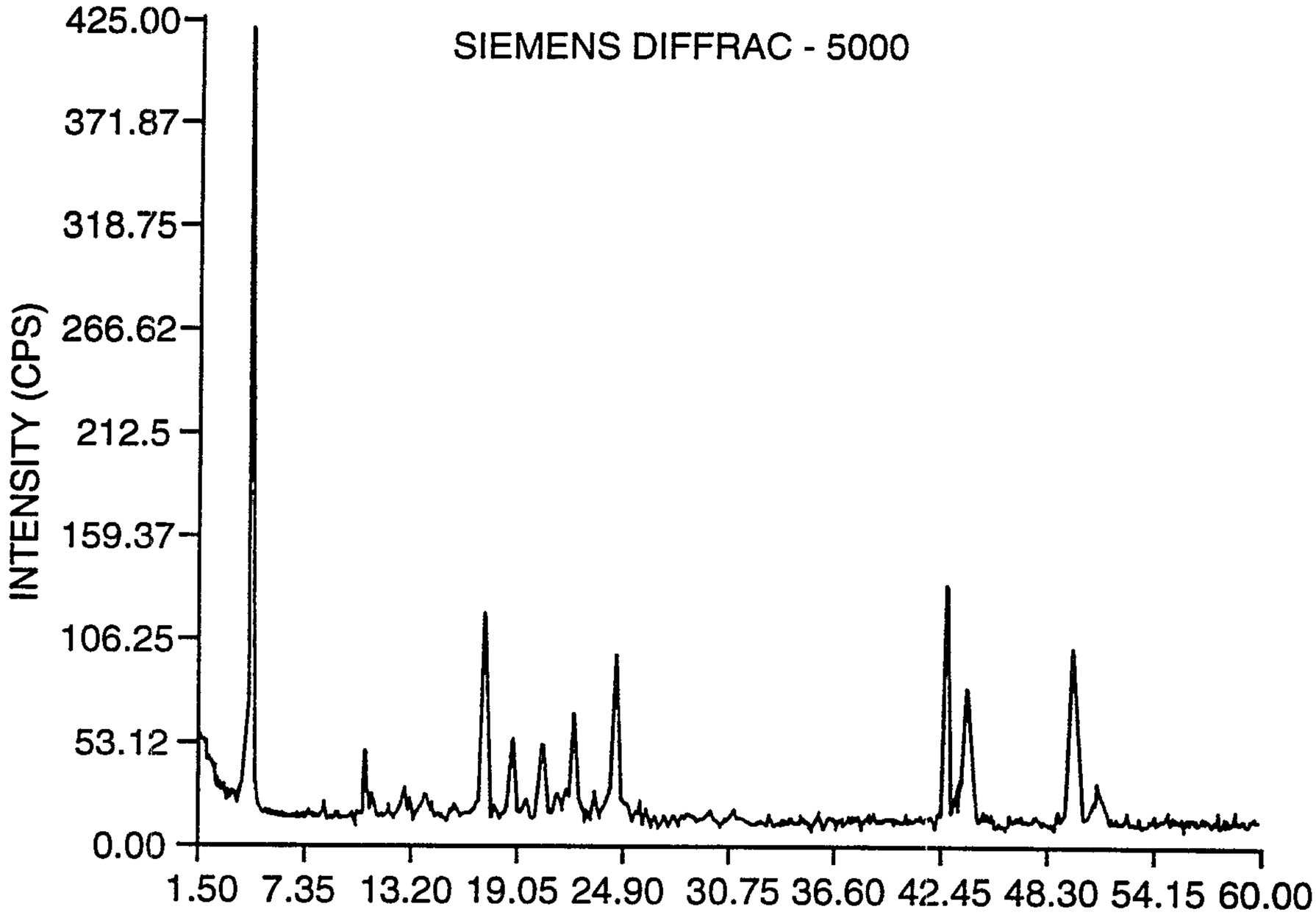


FIG.35.

SIEMENS DIFFRAC - 5000

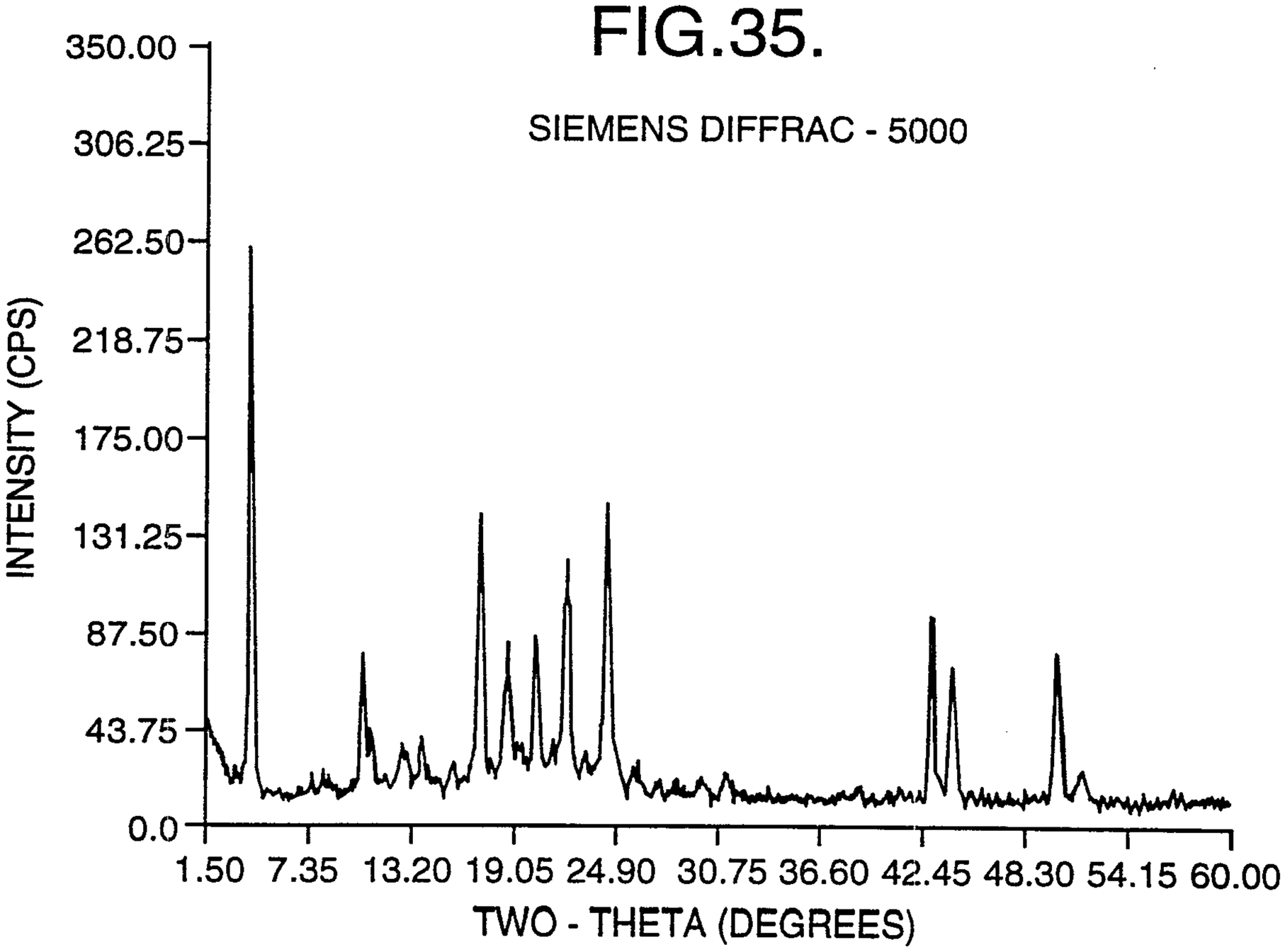


FIG.36.

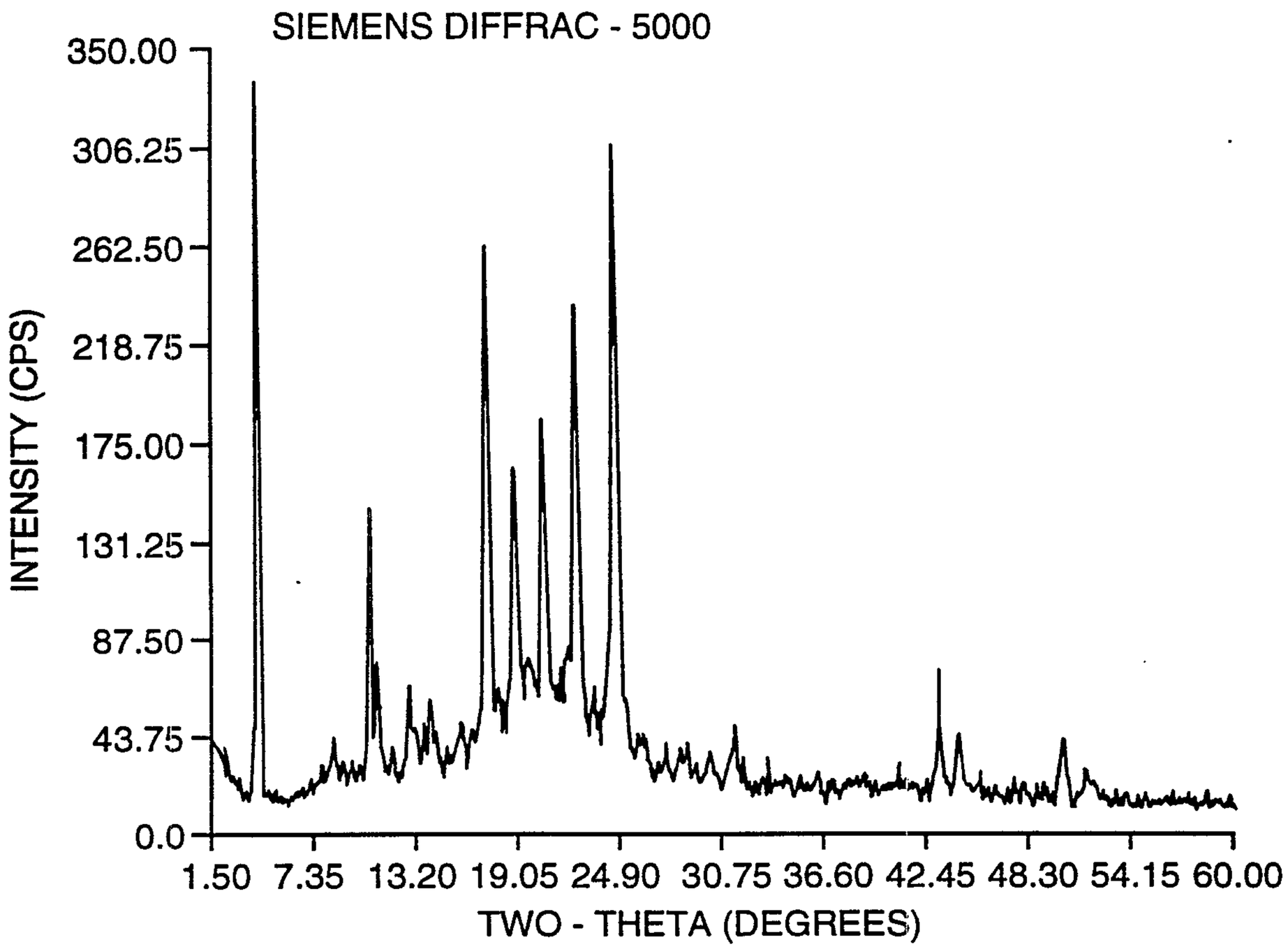

SIEMENS DIFFRAC - 5000
350.00
306.25
262.50
218.75
175.00
131.25
87.50
43.75
0.0
INTENSITY (CPS)
1.50 7.35 13.20 19.05 24.90 30.75 36.60 42.45 48.30 54.15 60.00
TWO - THETA (DEGREES)

Fig.37.

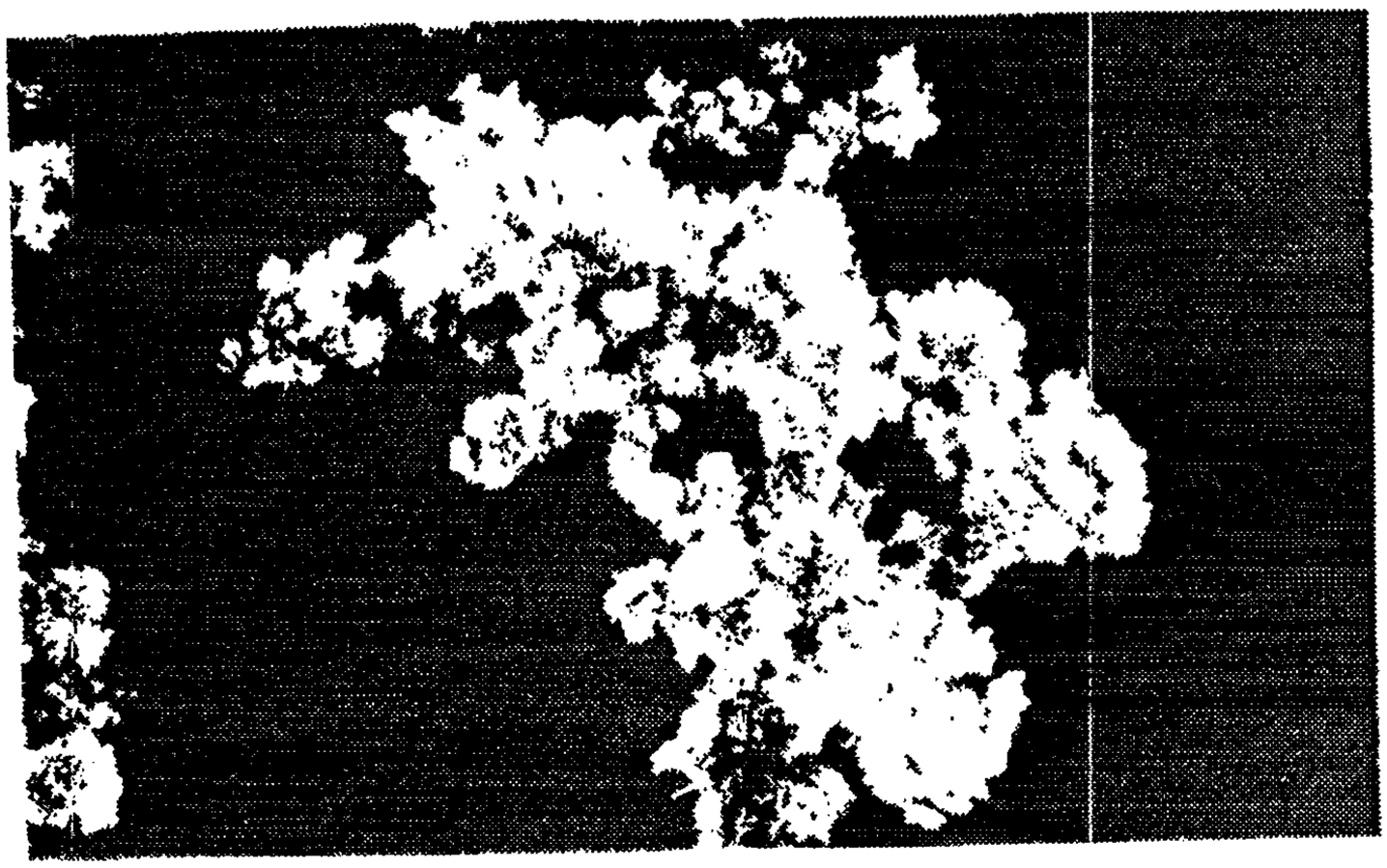


Fig.38.

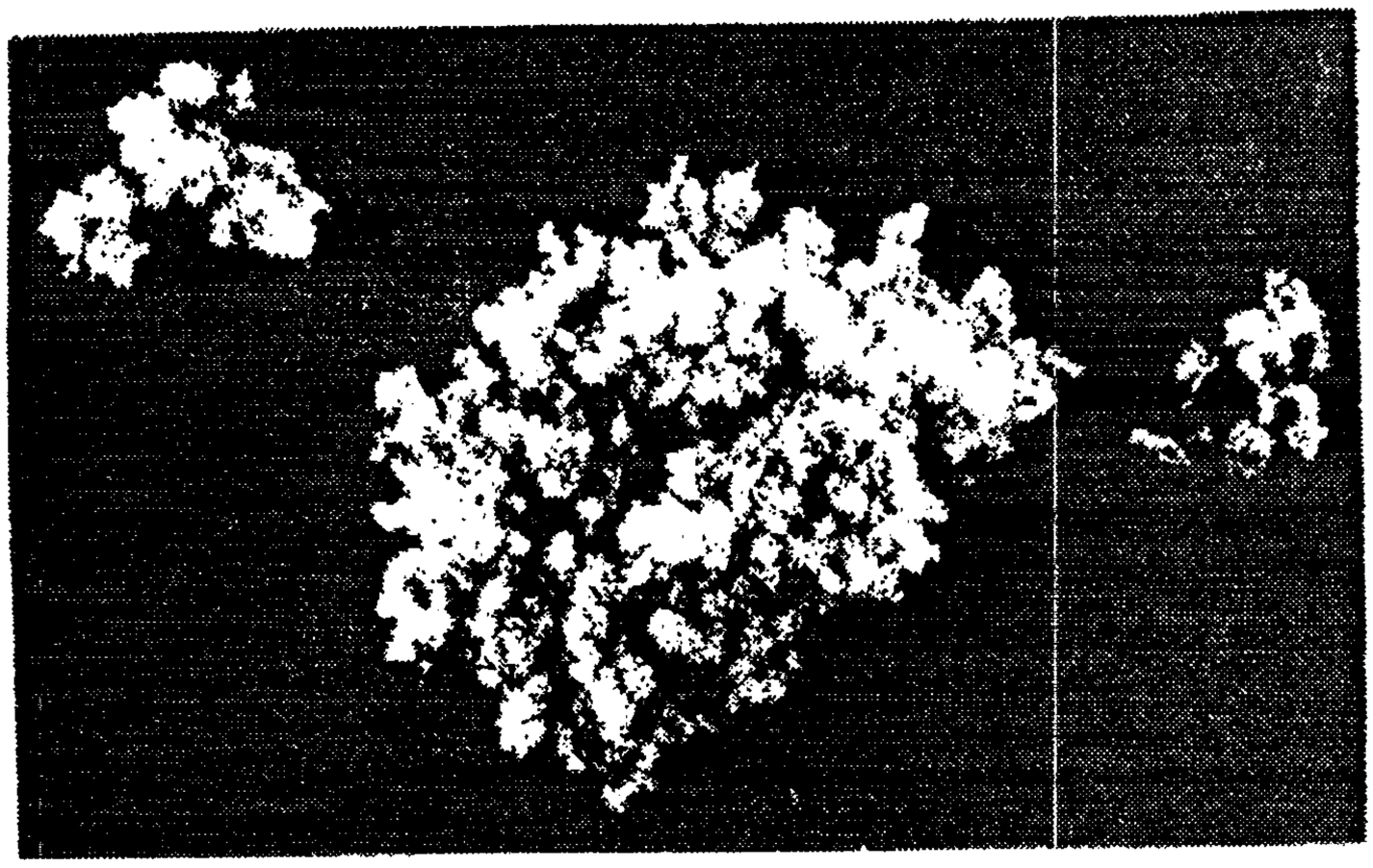
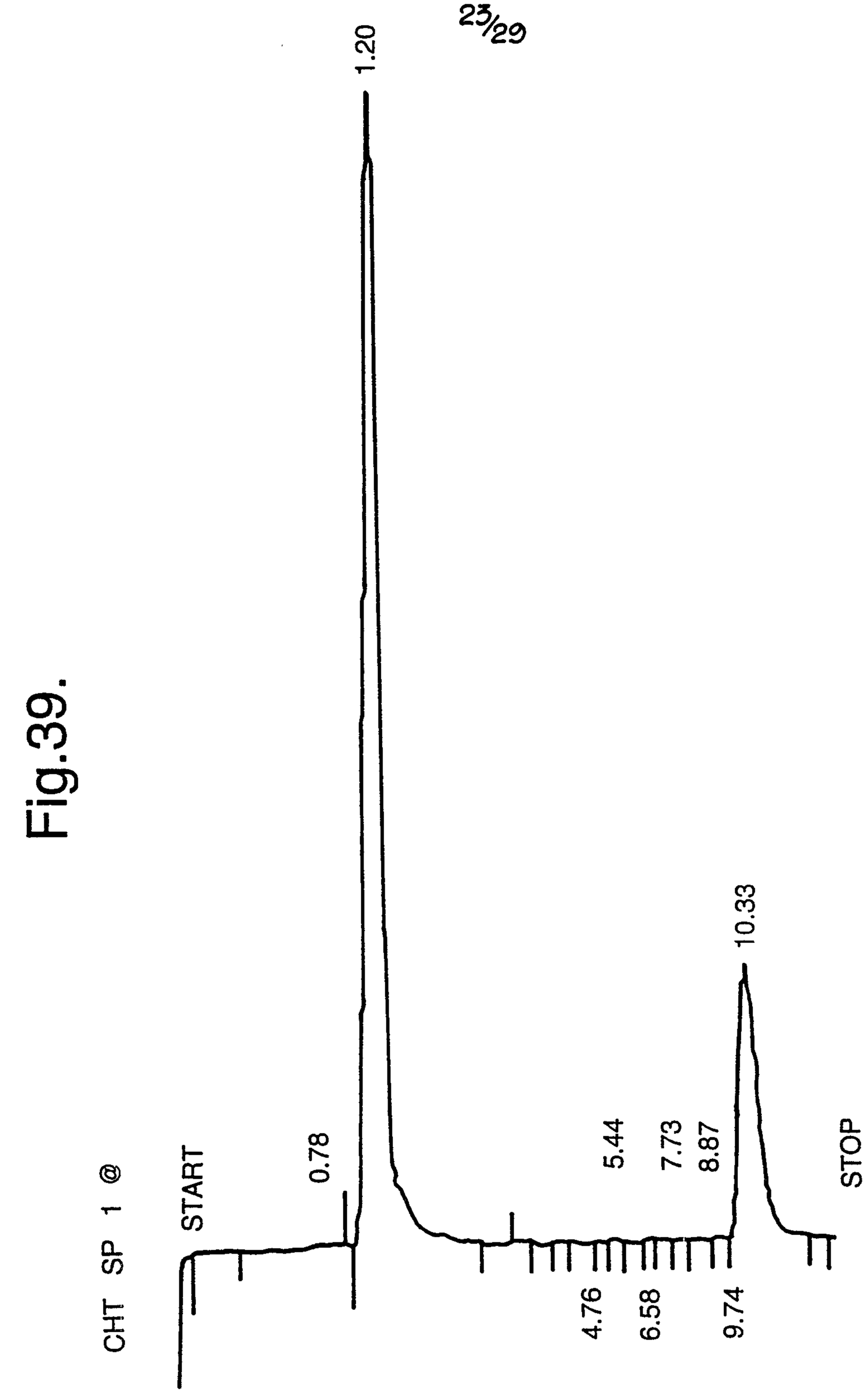


Fig.39.



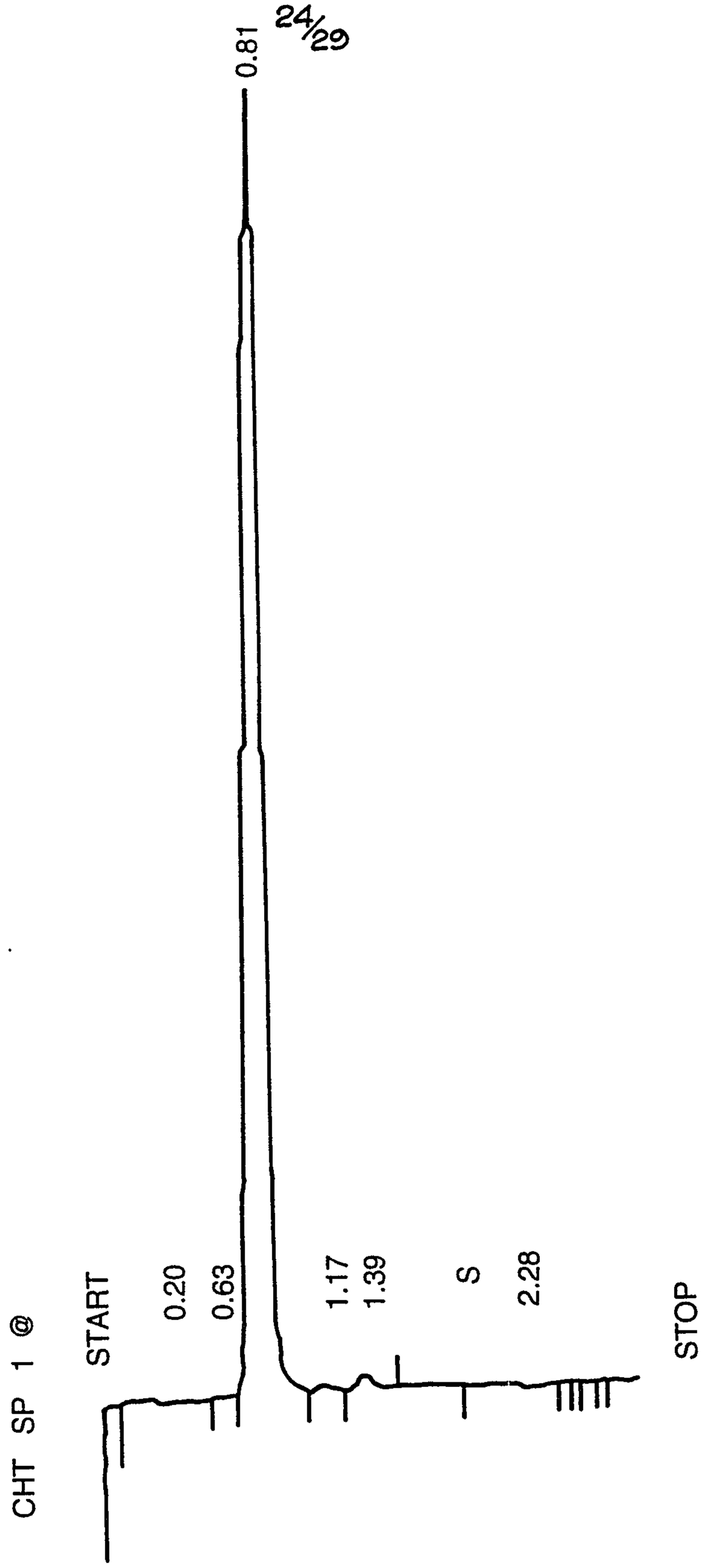


Fig.40

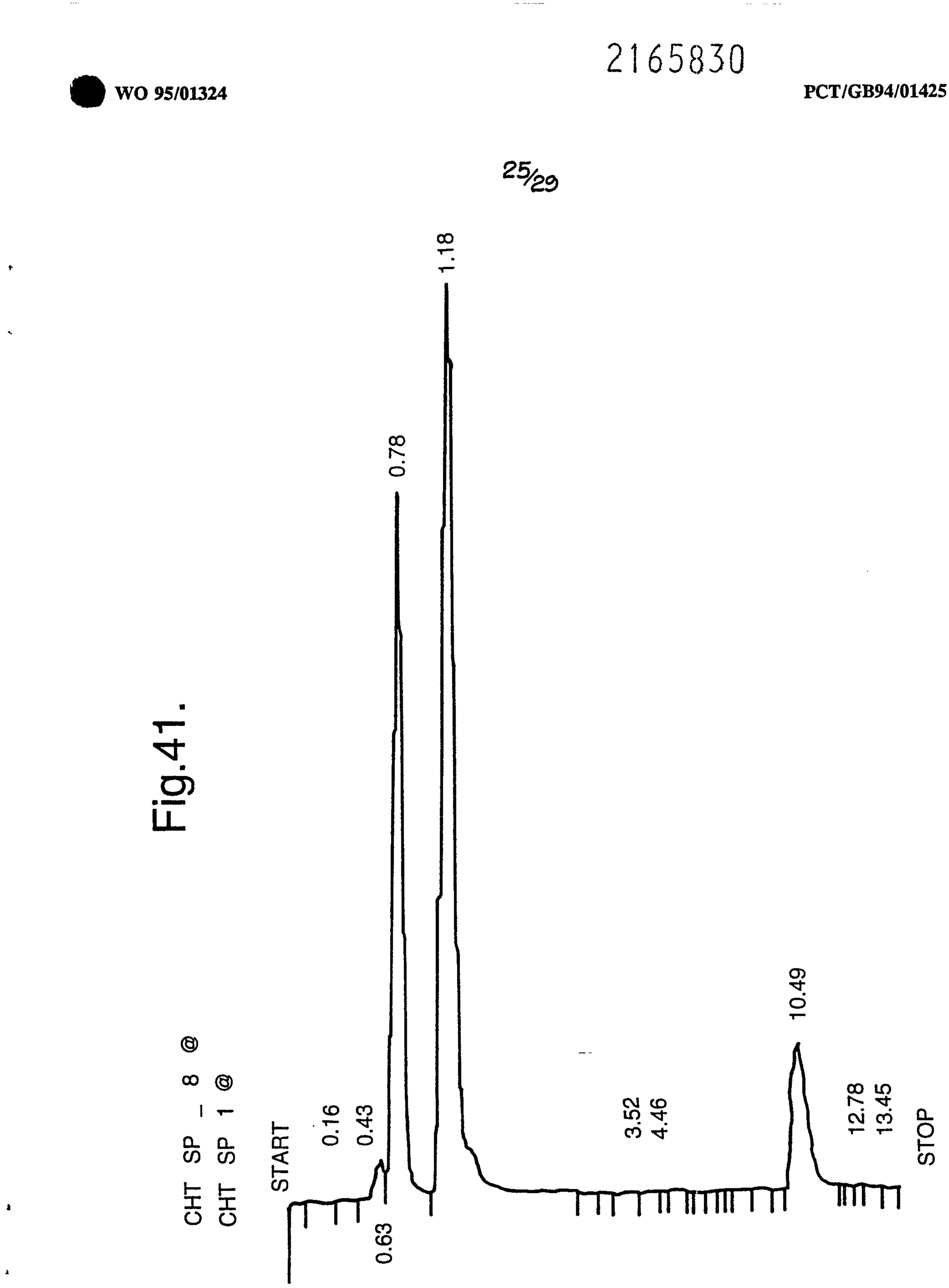

CHT SP _ 8 @
CHT SP 1 @
START
0.16
0.43
0.63
0.78
1.18
3.52
4.46
10.49
12.78
13.45
STOP

Fig.41.

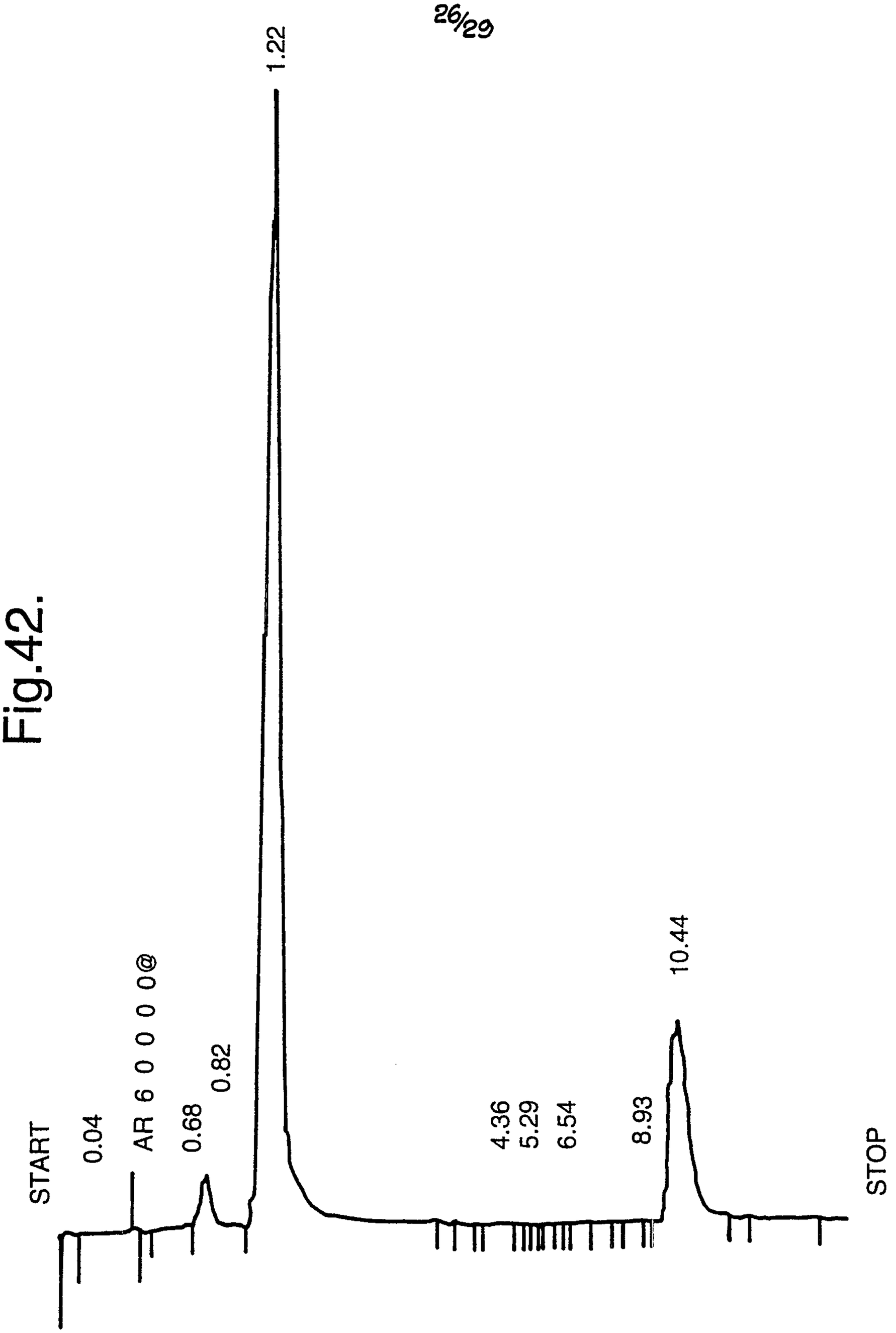


Fig.42.

Fig.43.

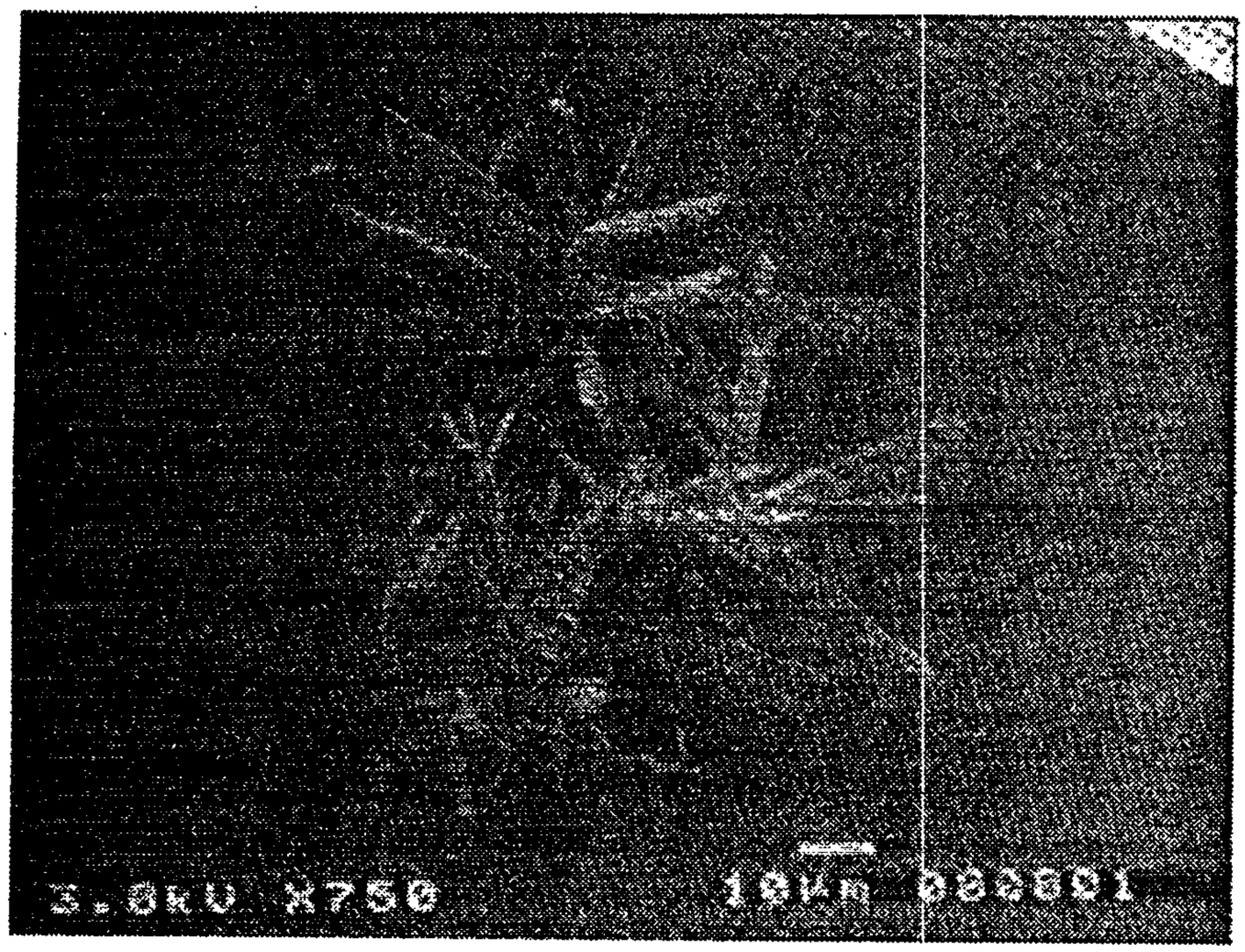


Fig.45.

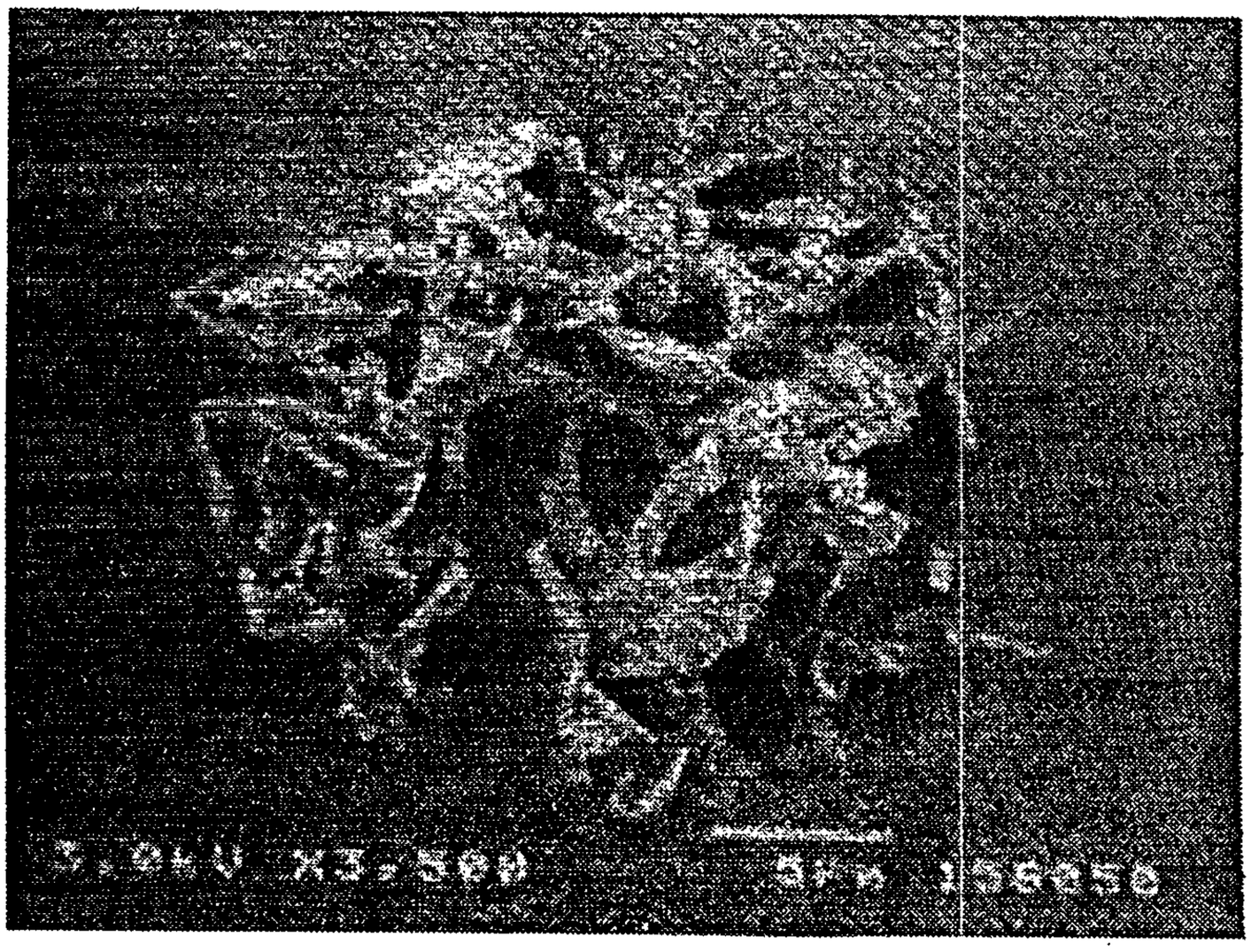


FIG.44.

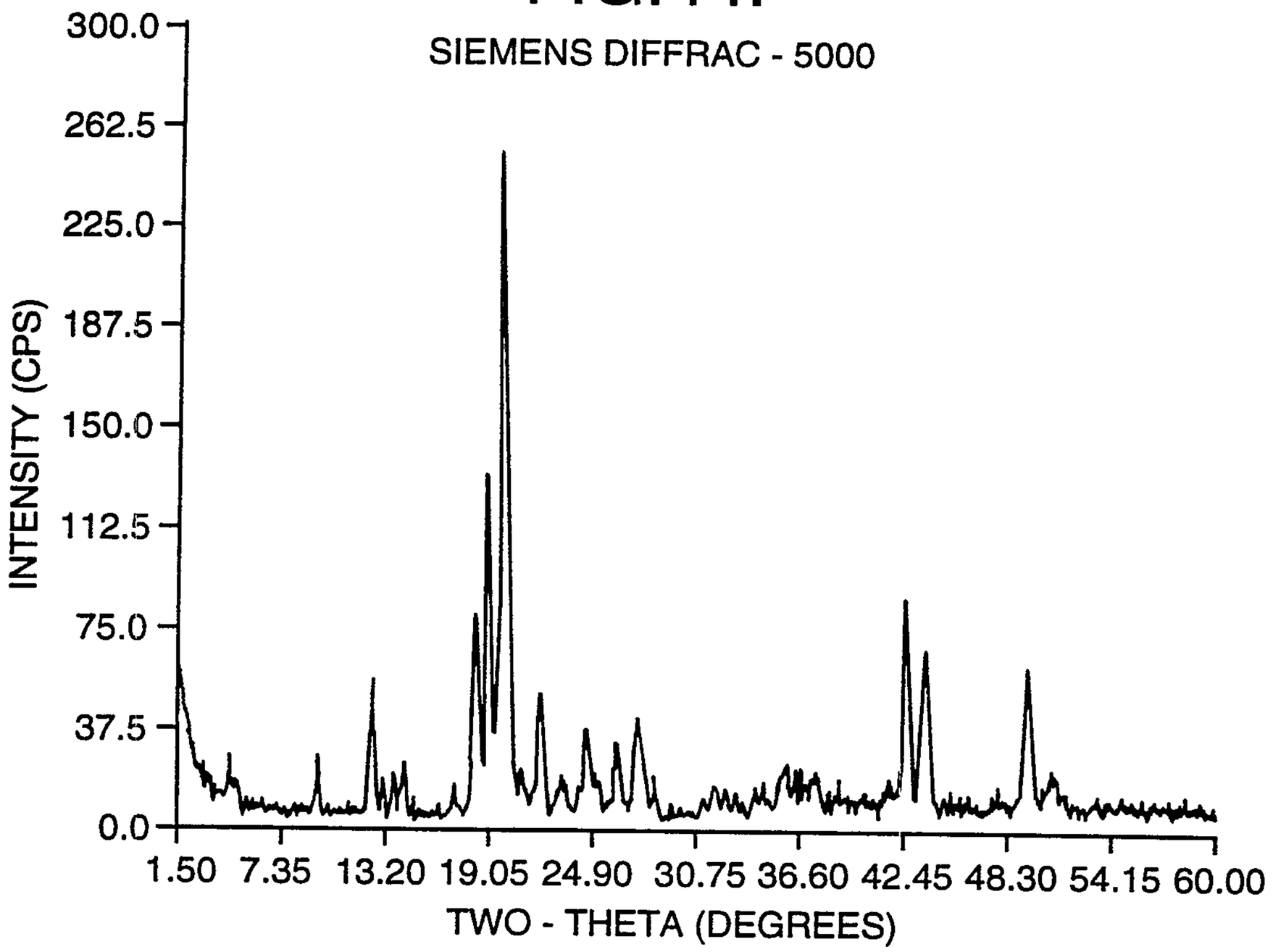

SIEMENS DIFFRAC - 5000
INTENSITY (CPS)
300.0
262.5
225.0
187.5
150.0
112.5
75.0
37.5
0.0
1.50 7.35 13.20 19.05 24.90 30.75 36.60 42.45 48.30 54.15 60.00
TWO - THETA (DEGREES)

FIG.46.

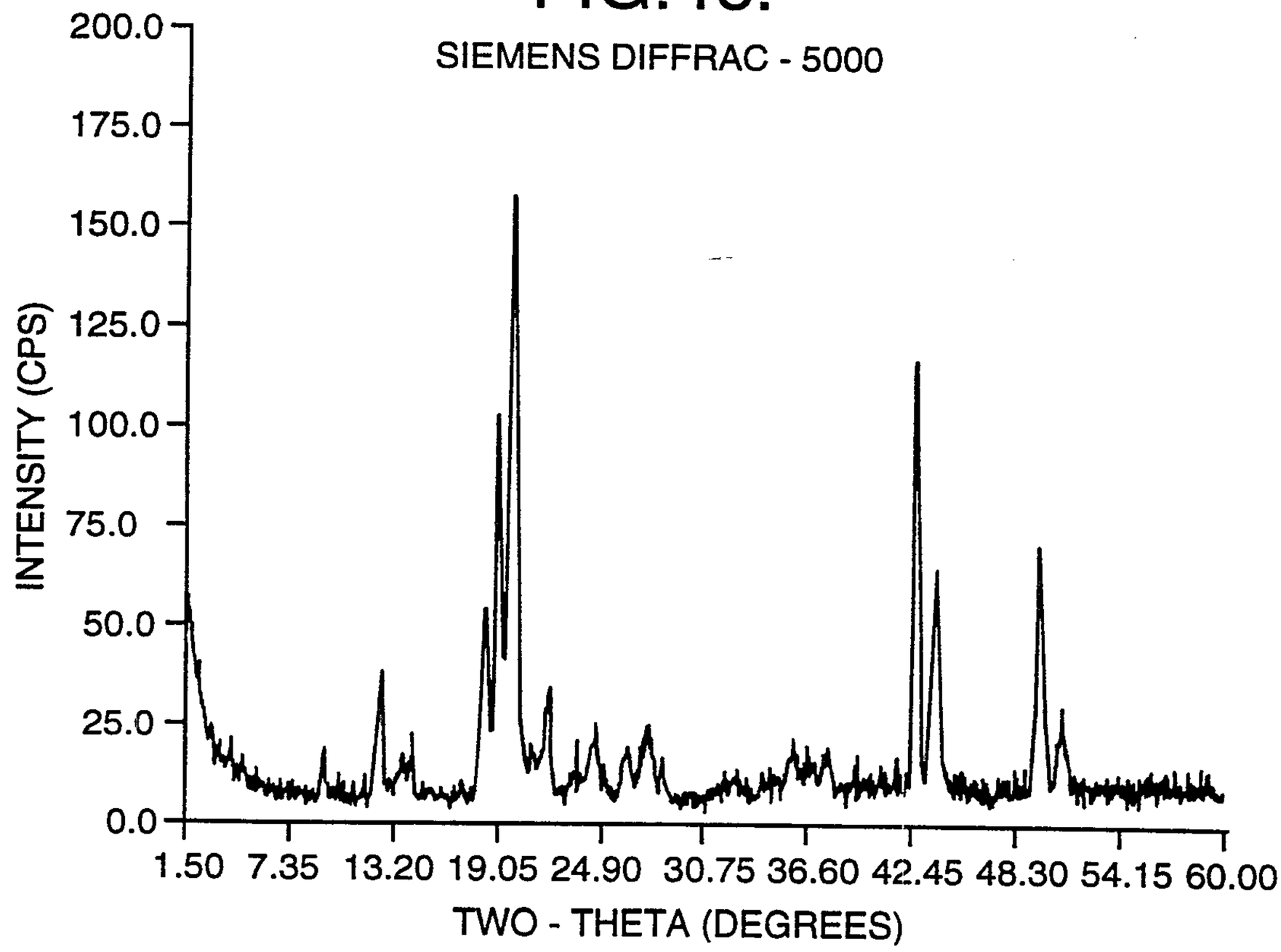

SIEMENS DIFFRAC - 5000
INTENSITY (CPS)
200.0
175.0
150.0
125.0
100.0
75.0
50.0
25.0
0.0
1.50 7.35 13.20 19.05 24.90 30.75 36.60 42.45 48.30 54.15 60.00
TWO - THETA (DEGREES)

FIG.47.

SIEMENS DIFFRAC - 5000

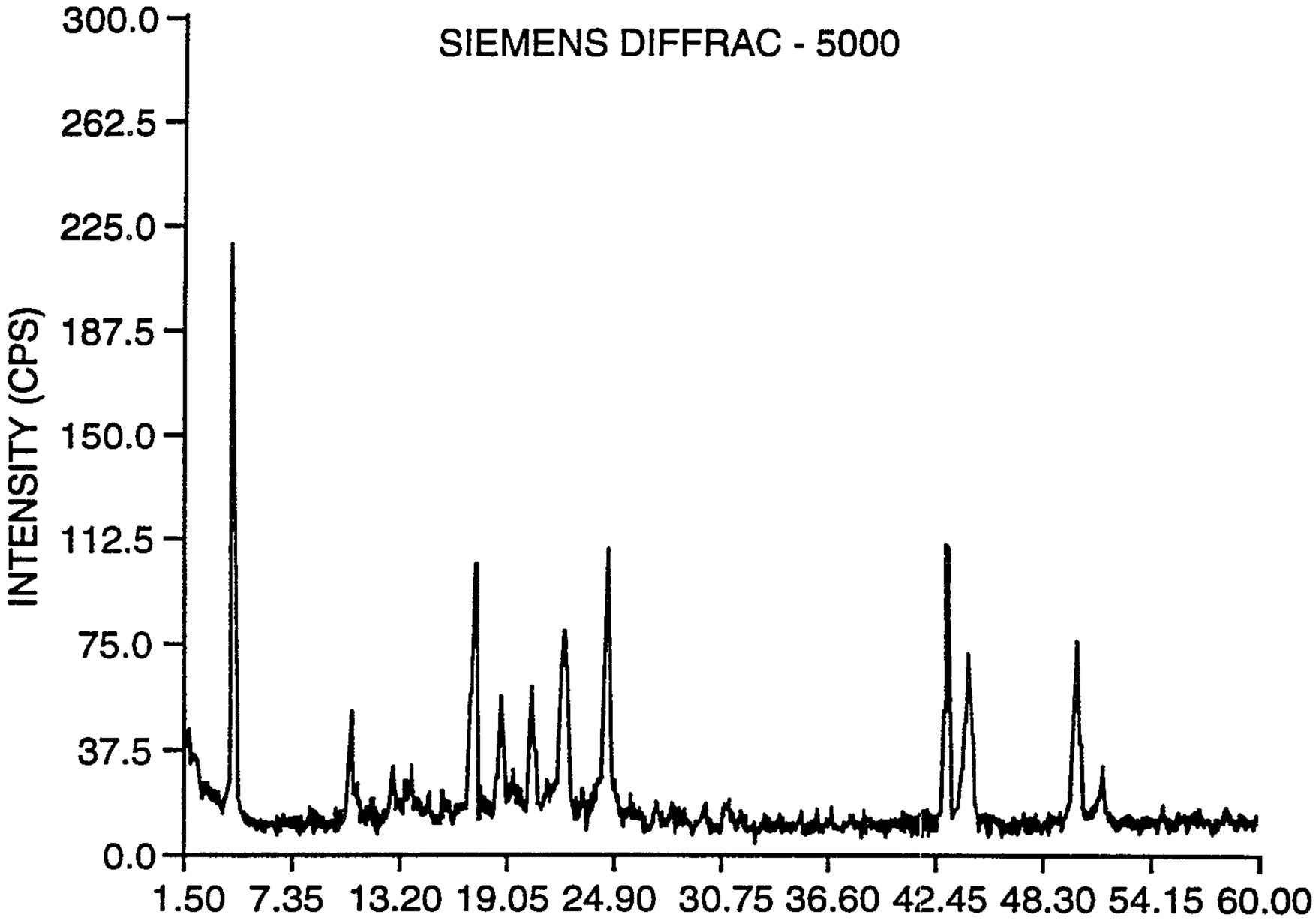


FIG.48.

SIEMENS DIFFRAC - 5000