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(54) Title: A PHARMACEUTICAL COMPOSITION CONTAINING AN ACTIVE AGENT THAT IS MAINTAINED IN SOLID AMORPHOUS FORM AND METHOD OF MAKING THE SAME

(57) Abstract: A pharmaceutical composition and process for producing a pharmaceutical composition that contains an active agent in solid amorphous form wherein the amorphous form of the active agent is maintained.

A PHARMACEUTICAL COMPOSITION CONTAINING AN ACTIVE AGENT THAT IS MAINTAINED IN SOLID AMORPHOUS FORM AND METHOD OF MAKING THE SAME

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to a pharmaceutical composition containing active agents which are maintained in a solid amorphous form.

2. Description of the Related Art

Drug substances, ranging from slightly or sparingly soluble to insoluble, have been found to decrease in crystallinity when mixed with various polymers and diluents. For example, in Sekizaki et al., *Chem. Pharm. Bull.*, 43(6):988-993 (1995), it was found that ibuprofen became amorphous when the crystalline powder was mixed with polyvinylpyrrolidone. In Kaneniwa et al. *Chem. Pharm. Bull.*, 26(9):2734-2743 (1978), a decrease in crystallinity was observed when amobarbital was treated in the presence of diluents. This decrease in crystallinity can enhance the solubility, dissolution rates and bioavailability of these substances.

The amorphous form of drug substances, however, are generally unstable, and can convert to a crystalline form. Some investigators have attempted to stabilize the amorphous form of drug substances by utilizing solid dispersion techniques. For example, in Imaizumi et al., *Chem. Pharm. Bull.*, 31(7):2510-2512 (1983), the stability of the amorphous form of indomethacin was enhanced by solid dispersion of the indomethacin in polyvinylpolypyrrolidone. Additionally, in Thakkar et al., *J. Pharm. Pharmac.*, 29:783-784 (1977), it was reported that the conversion to a crystalline state was effectively prevented when nabilone was dispersed in the water-soluble matrix of polyvinylpyrrolidone.

United States Patent No. 5,672,612, issued to Ronsen et al. on September 30, 1997, discloses the preparation of an amorphous form of paroxetine hydrochloride. Unlike the present invention, the Ronsen et al. patent, discloses combining paroxetine free base with a hydrochloric acid/ethanol solution and drying the product. Thus, the Rosen et al. patent does not address the problem solved by the present invention, that is converting a crystalline form of an active agent into a stable amorphous form.

WO 99/00131, published on January 7, 1999, teaches a process for preparing a solid state dispersion of paroxetine or its acid addition salts using a solvent or fusion process. In the solvent method, paroxetine free base is dissolved in a polymer/solvent solution, contacted with dry hydrochloride gas and then the non-aqueous solvent is removed by evaporation under vacuum. Preparation of a solid state dispersion, by the fusion technique, is taught to involve mixing a polymer with paroxetine free base, melting the mixture, contacting the melt with dry hydrogen chloride and then cooling the mixture. WO 99/00131 does not teach the use of a complexing agent to reduce and/or destroy the crystallinity of the crystalline form of an active drug nor does it teach the use of a co-solvent to prevent and/or reduces recrystallization.

Despite certain attempts, there still exists a need in the art for a pharmaceutical composition containing an active agent in a solid amorphous form wherein the active agent is maintained in such a form.

BRIEF SUMMARY OF THE INVENTION

It has been discovered that pharmaceutically active agents, in crystalline form, can be combined with a complexing agent and a co-solvent in order for the active agents to be converted to and maintained in a solid amorphous form.

Thus, one aspect of the present invention is a pharmaceutical composition comprising:

an active agent in solid amorphous form,

a complexing agent, and

a non-volatile co-solvent;

wherein the complexing agent converts the active agent from crystalline form to solid amorphous form, and the active agent, in the absence of the co-solvent, can recrystallize in the presence of the complexing agent.

A first preferred embodiment of the invention is that the active agent is a drug substance, preferably in crystalline form prior to its conversion to amorphous form. More preferably, the active agent is paroxetine, salts of paroxetine, spironolactone, etodolac, diclofenac or salts of diclofenac.

A second preferred embodiment of the invention is that the complexing agent is selected from the group consisting of crospovidone, povidone, cyclodextrin and a combination thereof.

A third preferred embodiment of the invention is that the non-volatile co-solvent is compatible with the active agent and miscible with the solvent. A more preferred embodiment is that the co-solvent is polyethylene glycol.

A fourth preferred embodiment is that the solvent is either an organic and volatile substance or water. An even more preferred embodiment is that the organic and volatile solvent is selected from the group consisting of ethanol, methanol, acetone, methylene chloride and a combination thereof.

An additional aspect of the invention is a pharmaceutical composition comprising:

paroxetine hydrochloride in a solid amorphous form,

a complexing agent selected from the group consisting of crospovidone, povidone, cyclodextrin and a combination thereof, and

polyethylene glycol 300.

A further aspect of the invention is a method for producing a pharmaceutical composition which comprises an active agent that is maintained in a solid amorphous form, comprising:

mixing a crystalline form of an active agent with a solvent;

adding a complexing agent and a co-solvent to the mixture; and

removing the solvent from the mixture so as to obtain the active agent in solid amorphous form.

Another aspect of the invention is a method for producing a pharmaceutical composition which comprises paroxetine hydrochloride that is maintained in a solid amorphous form, comprising:

mixing a crystalline form of paroxetine hydrochloride with ethanol;

adding a complexing agent selected from the group consisting of crospovidone, povidone, cyclodextrin and a combination thereof, and polyethylene glycol 300 to the mixture; and

removing the ethanol from the mixture so as to obtain the paroxetine hydrochloride in solid amorphous form.

With the foregoing and other objects, advantages and features of the invention that will become hereinafter apparent, the nature of the invention may be more clearly understood by reference to the following detailed description and to the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 represents the results of DSC run of paroxetine hydrochloride anhydrate showing a peak at 115° C, the melting point of the crystal.

Figure 2 represents the results of a DSC run on a sample containing a 1:3 ratio of paroxetine hydrochloride:crospovidone (Sample 1).

Figure 3 represents the results of a DSC run on a sample containing a 1:3:1 ratio of paroxetine hydrochloride:crospovidone:PEG 300 (Sample 2).

Figure 4 represents the results of a DSC run on a sample containing a 1:10 ratio of paroxetine hydrochloride:crospovidone (Sample 3).

Figure 5 represents the results of a DSC run on a sample containing a 1:10:1 ratio of paroxetine hydrochloride:crospovidone:PEG 300 (Sample 4).

Figure 6 represents the results of a DSC run on a sample containing a 1:3 ratio of paroxetine hydrochloride:crospovidone that was mixed with a spatula (Sample 5).

Figure 7 represents the results of a DSC run on a sample containing a 1:2:1:1 ratio of paroxetine hydrochloride:crospovidone:povidone:PEG 300.

Figure 8 represents the results of DSC run of spironolactone showing a melting range of the crystal at 198-207°C, the melting point of the crystal.

Figure 9 represents the results of a DSC run on a sample containing a 1:3 ratio of spironolactone:crospovidone (Sample 6).

Figure 10 represents the results of a DSC run on a sample containing a 1:3:1 ratio of spironolactone:crospovidone:PEG 300 (Sample 7).

Figure 11 represents the results of DSC run of etodolac showing a melting range of the crystal at 146-151°C.

Figure 12 represents the results of a DSC run on a sample containing a 1:1:3:1 ratio of etodolac:povidone:crospovidone:PEG 300.

Figure 13 represents the results of DSC run of diclofenac sodium showing a melting range of the crystal at 283-285°C.

Figure 14 represents the results of a DSC run on a sample containing a 1:1:3:1 ratio of diclofenac sodium:povidone:crospoviddone:PEG 300.

DETAILED DESCRIPTION OF THE INVENTION

The decrease in crystallinity of various drug substances can enhance the solubility, dissolution rates and bioavailability of these substances. Therefore, use of the amorphous form of these drug substances in pharmaceutical formulations is

often advantageous. The amorphous form of these drug substances, however, is unstable, and can convert to a crystalline form.

Despite the prior art which teaches that when the amorphous forms of indomethacin and nabilone were dispersed in either polyvinylpyrrolidone (also known as PVP or povidone) or polyvinylpolypyrrolidone (also known as PVPP or crospovidone) the amorphous state of the drug substances were stabilized, the inventors of the subject application have determined that a number of active agents in their amorphous form can recrystallize in the presence of a complexing agent. The inventors have surprisingly found that active agents in solid amorphous form, which can recrystallize in the presence of a complexing agent, can be stabilized or maintained in its amorphous state by combining the amorphous form of the active agent with a complexing agent and a co-solvent.

This invention is applicable to any solid active agent. The term active agent is defined as an active ingredient that is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in humans or other animals. Such active agents include, but are not limited to, crystalline forms of active agents which have appreciable solubilities in a solvent wherein the solvent is ultimately removed from the final product. The solvent is preferably either an organic and volatile substance or water. More preferably, the organic and volatile solvent includes, but is not limited to, ethanol, methanol, acetone, methylene chloride or a combination thereof. The active agents of the present invention also include drug substances such as paroxetine, salts of paroxetine (e.g., acid addition salts such as paroxetine hydrochloride), spironolactone, etodolac, diclofenac and salts of diclofenac (e.g., sodium or potassium salts of diclofenac). Other active agents will be recognized by those skilled in the art.

The active agent is present in a pharmacologically effective amount. A pharmacologically effective amount, as used herein, is any amount of active agent

sufficient to provide pharmacological activity or otherwise sufficient to affect the structure or function of the body in humans or other animals.

The specific pharmacological activity will depend upon the particular active agent which is utilized. For instance, paroxetine and its salts, e.g., acid addition salts, are known to have an anti-depressant effect, utility as an analgesic, and an anti-obesity effect. The indications include depression, obsessive compulsive disorders and panic disorders. Spironolactone, for example, acts both as a diuretic and as an antihypertensive drug. The indications include primary hyperaldosteronism, edematous conditions, essential hypertension and hypokalemia. The drug substance etodolac is, for instance, a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic and antipyretic activies. The indications include acute and long term use for osteoarthritis and rheumatoid arthritis and management of pain. Diclofenac and its salts are also nonsteroidal anti-inflammatory drugs that exhibit the same properties as listed for etodolac. Diclofenac and its salts are used to treat osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, management of pain and primary dysmenorrhea. Other pharmacological activities will be recognied by one skilled in the art.

Determination of an effective amount depends on various factors well known to those skilled in the art such as the nature and severity of the condition to be treated, the frequency and route of administration, and the weight of the human or animal requiring treatment. However, it is believed that an amount from about 0.01 to 100 mg/kg of body weight per day of any one of the preferred active agents should be effective for producing the intended pharmacological effect.

The pharmaceutical composition of the present invention can be presented as a unit dose. Thus, a unit dose of the pharmaceutical composition containing any one of the preferred active agents can generally contain from about 0.1 to 1000 mg of the active agent. Such unit dose compositions may be administered once or more times a day.

It is to be understood that the amounts set forth herein are exemplary and they do not, to any extent, limit the scope or practice of the invention.

The term "complexing agent" as defined in the present invention is a substance which associates with the active agent through either chemical binding or physical interaction to reduce or destroy the crystallinity of the active agent. Preferrably, the complexing agent is crospovidone, povidone, cyclodextrin or any combination thereof. This invention is not limited, however, to a particular complexing agent and other complexing agents will be apparent to those skilled in the art.

A preferred amount of complexing agent to be used in the present invention ranges from 10/1 - 1/100 wt/wt (drug/complexing agent). Parameters which may affect the ratio include molecular weights of the drug and the complexing agent as well as the molecular structure of the drug and the complexing agent.

Further, as used herein, a co-solvent is defined as a substance which has an appreciable solubility for the drug substance and which enhances the complexation and/or stabilizes the complex formed. Generally, the co-solvent should be non-volatile. Non-volatile means that there should not be a significant amount of co-solvent loss under processing conditions, including the process to remove the solvent. Preferably, the co-solvent should be compatible with the active agent and miscible with the solvent. Such co-solvents include, but are not limited to, polyethylene glycols, propylene glycol, glycerol, liquid petrolatum and lauryl alcohol. Other co-solvents will be apparent to those skilled in the art.

A preferred amount of co-solvent to be used in the present invention ranges from 10/1 - 1/10 wt/wt (drug/co-solvent). The range of co-solvent may depend on the type of drug, complexing agent and co-solvent used.

The pharmaceutical compositions according the present invention can also include other inert material or additives known as a pharmaceutically acceptable

excipient. Pharmaceutically acceptable excipients are generally present to facilitate manufacturing, packaging and handling of the drug. These well known and art recognized excipients include, for example, fillers or diluents, binders or granulators, lubricants, glidants, disintegrants and coloring, flavoring and sweetening agents. Other excipients will be apparent to those of skill in the art.

The pharmaceutical compositions of the present invention are preferably in solid dosage form. Any well known tabletting procedure, encapsulating procedure or other procedure to prepare a solid dosage form can be employed herein.

The following examples are presented in order to more fully illustrate the preferred embodiments of the invention. They should in no way be construed, however, as limiting the scope of the invention.

EXAMPLE I

The following procedure was used to prepare a solid amorphous form of paroxetine hydrochloride. To begin, 10 grams of anhydrous paroxetine hydrochloride were added to 120 grams of ethanol. The sample was stirred and heated to 45°C. Stirring was continued until the paroxetine hydrochloride was fully dissolved. Crospovidone, 30 grams of Polyplasdone XL (BASF; Mount Olive, NJ), was added to the paroxetine hydrochloride solution to form a slurry. The slurry was stirred and heated at 45°C for 24 hours. Polyethylene glycol, 10 grams of PEG 300 (Dow Chemicals; Midland, Michigan), was added to the slurry and the sample was mixed well. The sample was then dried in an oven at 55°C to remove the ethanol. The weight of the sample was monitored periodically until a constant weight was achieved. The sample was removed from the oven and ground to obtain a solid material containing of the amorphous form of paroxetine hydrochloride.

EXAMPLE II

A solid paroxetine hydrochloride containing drug complex, wherein the paroxetine hydrochloride is maintained in an amorphous form, is as follows:

Paroxetine Hydrochloride	11.5 mg
Ethanol	115 mL
Povidone (Plasdone K 29-32 [ISP Technologies; Texas City, TX])	11.5 mg
Crospovidone (Polyplasdone XL [BASF; Mount Olive, NJ])	23 mg
Polyethylene Glycol (PEG 300 [Dow Chemicals; Midland, Michigan])	11.5 mg

A solid spironolatone containing drug complex, wherein the spironolactone is maintained in an amorphous form, is as follows:

Spironolactone	25 mg
Ethanol	250 mL
Povidone (Plasdone K 29-32 [ISP Technologies; Texas City, TX])	25 mg
Crospovidone (Polyplasdone XL [BASF; Mount Olive, NJ])	50 mg
Polyethylene Glycol (PEG 300 [Dow Chemicals; Midland, Michigan])	25 mg

The above drug complexes can be prepared using the following steps. The ethanol (solvent) and the active agent are placed in a bowl of a high-shear mixer (Collette Gral), equipped with a heating jacket and connected to the source of heat. The set-point temperature of the heating medium is set to 50°C. The content of the bowl is heated, while the material is stirred, until all of the active agent is completely dissolved. The povidone is added to the bowl and stirred until it is completely dissolved. The crospovidone is then added and the bowl's content

is stirred for two hours. The polyethylene glycol is added next and the stirring continues for 30 minutes. The set-point temperature of the heating medium is set to 80°C (in the event that the solvent is water the set-point temperature of the heating medium would be set for 100°C) and the removal of the solvent is commenced under slight negative pressure, until the consistency of the material is such as to be suitable for transfer to the drying equipment (the solvent content is approximately 15% to 25%). The material is then placed in the drying equipment (a tray oven or a fluid-bed drier) and dried at the inlet air temperature set at 50°C, until the residual solvent content is less than 5%. The semi-dried material is milled using a comminuting mill (Fitzpatrick) equipped with a perforated plate with 0.093" diameter holes and set at 2,450 rpm (medium speed). The milled material is then returned back to the drying equipment and dried at 50°C until the residual moisture content is below 2%. The dried material is milled again through a perforated plate with 0.020" diameter holes with the mill being set at 4,600 rpm (high speed).

Alternative techniques can also be used to dry the complex. In addition to oven and fluid bed drying, the complex can be spray dried or vacuum microwave dried. Other methods will be readily recognized by those skilled in the art.

These next steps are optional. The milled granules are placed in a jacketed bowl of a Gral, PEG 8000 (Carbowax) is added and the content of the bowl is heated at 80°C, while mixing, until all of the particles are coated with PEG. The material is then discharged from the bowl, spread on ss trays and allowed to cool to room temperature. The cooled material is milled again through a perforated plate with 0.020" diameter holes with the mill being set at at 4,600 rpm (high speed).

Once the drug complex is formed, a final blend can be prepared which can either be compressed into tablets or filled into empty gelatin capsules. Final

blends containing the paroxetine hydrochloride-containing drug complex as well as the spironolactone-containing drug complex are as follows:

Paroxetine hydrochloride-containing drug complex	46 mg
microcrystalline cellulose (AVICEL PH 102)	45 mg
lactose anhydrous DT	50 mg
crospovidine	6 mg
colloidal silicon dioxide	2 mg
magnesium stearate	1 mg
TOTAL TABLET WEIGHT	*150 mg*

Paroxetine hydrochloride-containing drug complex	46 mg
dicalcium phosphate	95 mg
crospovidone	6 mg
colloidal silicon dioxide	2 mg
magnesium stearate	1 mg
TOTAL TABLET WEIGHT	*150 mg*

spironolactone-containing drug complex	75 mg
dibasic calcium phosphate	110 mg
crospovidone	12 mg
colloidal silicon dioxide	1 mg
magnesium stearate	2 mg
TOTAL TABLET WEIGHT	*200 mg*

The above tabletting ingredients are combined in a blender and mixed together to form a final blend. The blend is compressed into tablets which can be optionally color coated with an aqueous dispersion such as Opadry® (Colorcon). Alternatively, the final blend can be filled into empty gelatin capsules.

EXAMPLES III - IX

To demonstrate that the co-solvent prevents recrystallization of the active agent in the presence of the complexing agent, samples were prepared with and without PEG 300 and then differential scanning calorimetry (DSC) was carried out.

The DSC conditions were as follows:

- DSC instrument: Mettler Toledo DSC 821^e
- Heating rate: 20° C/minute
- Temperature range: 0° C - 250° C.

The DSC method as described in Imaizumi et al., *Chem. Pharm. Bull.*, 28:2565-2569 (1980) can also be employed for determining the degree of crystallinity of a compound. This article is hereby incorporated by reference in its entirety.

The samples used to run the DSC scans were prepared as follows.

Sample 1 - paroxetine hydrochloride:crospovidone = 1:3

Sample 2 - paroxetine hydrochloride:crospovidone:PEG 300 = 1:3:1

Preparation:

1. 0.5 grams of anhydrous paroxetine hydrochloride was mixed and dissolved in 15 grams of ethanol.
2. 1.5 grams of crospovidone was added to the solution to form a slurry. The slurry was stirred for 2 hours and then sat overnight at room temperature. The slurry was then divided into two equal parts, Sample 1 and Sample 2.

3. Sample 1 was dried in an oven at 45°C until the ethanol evaporated. The sample was ground and scanned on a DSC.
4. Prior to drying Sample 2, 0.25 grams of PEG 300 was added and mixed. The mixture was then dried at 45°C until the ethanol evaporated. The sample was ground and scanned on a DSC.

Sample 3 - paroxetine hydrochloride:crospovidone = 1:10

Sample 4 - paroxetine hydrochlorie:crospovidone:PEG 300 = 1:10:1

Preparation:

The above process was used to produce Samples 3 and 4 with the exception of the change in weight ratios.

Sample 5 - paroxetine hydrochloride:crospovidone = 1:3

Preparation:

Sample 5 is simply a 1:3 ratio of anhydrous paroxetine hydrochloride: crospovidone that was mixed with a spatula.

Sample 6 - spironolactone:crospovidone = 1:3

Sample 7 - spironolactone:crospovidone:PEG 300 = 1:3:1

Preparation:

1. 23 grams of spironolactone is added to 230 grams of ethanol. The solution is heated to 50°C and stirred until the drug is dissolved.
2. 69 grams of crospovidone and an additional 100 grams of ethanol are added to the solution to form a slurry. The mixture is stirred for 24 hours at 50°C. The slurry is divided into two equal parts, Sample 1 and Sample 2.
3. Sample 1 is dryed at 60°C until the ethanol has evaporated. The sample is ground and scanned on a DSC.

4. Prior to drying Sample 2, 23 grams of PEG 300 is added and mixed. The mixture is then dryed at 60°C until the ethanol has evaporated. The sample is ground and scanned on a DSC.

The results of the DSC runs, as described above, are set forth in Figures 2-6 and 9-10. Figures 1 and 8 demonstrate what the scans of DSC runs look like for the crystalline form of paroxetine hydrochloride and spironolactone. As can be seen from the DSC scans of Figures 2, 4 and 6, where the co-solvent is absent, small peaks are present which indicate re-crystallization. In contrast, the samples where the co-solvent and complexing agent was used, Figures 3 and 5, no peaks are shown on the scan. The absence of peaks at the melting temperature of the drug crystals indicates the absence of drug crystals in the sample. Thus, the samples containing both the co-solvent and the complexing agent are maintained in a solid amorphous form.

EXAMPLE X

A solid etodolac-containing drug complex (a 1:1:3:1 ratio of etodolac:povidone:crospovidone:PEG 300), was prepared in the following manner.

800 g of micronized etodolac and 8,000 g of ethanol were places in a 25 L Collette Gral bowl and mixed while warming to 50°C, until all of the drug was dissolved. 800 g of Povidone USP K 29-32 was added and mixed until completely dissolved. 1,600 g of Crospovidone NF was added and mixed for 2 hours while maintaining the termperature at 50°C. 800 g of PEG 300 was added and mixed for 30 minutes. The heating temperature was increased to 80°C and the bulk of alcohol was evaporated. Semi-dry material was placed in a tray oven and dried at 40°C for approximately 18 hours. The material was then milled through a perforated plate with 0.065" diameter holes using a Fitzpatrick comminuting mill. This material was then placed back in the oven for an additional drying, until the

residual solvent content is below 2%. This material is then milled through a perforated plate with 0.020" diameter holes.

A sample of the resultant complex was tested by DSC and the results are set forth in Figure 12. The Figure shows no peaks, as compared to the crystalline form of the active drug (Figure 11), thereby indicating that the active drug is maintained in solid amorphous form.

EXAMPLE XI

A solid diclofenac sodium-containing drug complex (a 1:1:3:1 ratio of diclofenac sodium:povidone:crospovidone:PEG 300), was prepared in the following manner.

1000 g of diclofenac sodium and 10,000 g of purified water were places in a 25 L Collette Gral bowl and mixed while warming to 65°C, until all of the drug was dissolved. 1,000 g of Povidone USP K 29-32 was added and mixed until completely dissolved. 2,000 g of Crospovidone NF was added and mixed for 2 hours while maintaining the termperature at 65°C. 1,000 g of PEG 300 was added and mixed for 30 minutes. The heating temperature was increased to 105°C and the bulk of water was evaporated. Semi-dry material was placed in a tray oven and dried at 55°C for approximately 18 hours. The material was then milled through a perforated plate with 0.065" diameter holes using a Fitzpatrick comminuting mill. This material was then placed back in the oven for an additional drying, until the residual solvent content is below 2%. This material is then milled through a perforated plate with 0.020" diameter holes.

A sample of the resultant complex was tested by DSC and the results are set forth in Figure 14. The Figure shows no peaks, as compared to the crystalline form of the active drug (Figure 13), thereby indicating that the active drug is maintained in solid amorphous form.

While the invention has been described in terms of various preferred embodiments, a person skilled in the art will appreciate that various modifications, substitutions, omissions and changes can be made without departing from the spirit thereof. Accordingly, it is intended that the scope of the present invention be limited solely by the scope of the following claims, including equivalents thereof. Further, all of the publications and patents cited herein are incorporated by reference in their entirety.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising:

an active agent in solid amorphous form,

a complexing agent, and

a non-volatile co-solvent;

wherein the complexing agent converts the active agent from crystalline form to solid amorphous form, and the active agent, in the absence of the co-solvent, can recrystallize in the presence of the complexing agent.

2. The composition of claim 1, wherein the active agent is paroxetine.

3. The composition of claim 1, wherein the active agent is paroxetine hydrochloride.

4. The composition of claim 1, wherein the active agent is spironolactone.

5. The composition of claim 1, wherein the active agent is etodolac.

6. The composition of claim 1, wherein the active agent is diclofenac.

7. The composition of claim 1, wherein the active agent is a sodium or potassium salt of diclofenac.

8. The composition of claim 1, wherein the complexing agent is selected from the group consisting of crospovidone, povidone, cyclodextrin and a combination thereof.

9. The composition of claim 1, wherein the complexing agent is crospovidone.

10. The composition of claim 1, wherein the crystalline form of the active agent is mixed with a solvent which is ultimately removed from the composition.

11. The composition of claim 1, wherein the solvent is an organic and volatile substance or water.

12. The composition of claim 1, wherein the solvent is selected from the group consisting of ethanol, methanol, acetone, methylene chloride and a combination thereof.

13. The composition of claim 1, wherein the solvent is ethanol.

14. The composition of claim 1, wherein the non-volatile co-solvent is compatible with the active agent and miscible with the solvent.

15. The composition of claim 1, wherein the non-volatile co-solvent is polyethylene glycol.

16. The composition of claim 1, wherein the non-volatile co-solvent is polyethylene glycol 300.

17. The composition of claim 1, wherein the pharmaceutical composition is in a solid dosage form.

18. A pharmaceutical composition comprising:

paroxetine hydrochloride in a solid amorphous form,

a complexing agent selected from the group consisting of crospovidone, povidone, cyclodextrin and a combination thereof, and

polyethylene glycol 300;

wherein the complexing agent converts paroxetine hydrochloride from crystalline form to solid amorphous form.

19. The composition of claim 18, wherein the paroxetine hydrochloride is maintained in a solid amorphous form.

20. A method for producing a pharmaceutical composition which comprises an active agent that is maintained in a solid amorphous form, comprising:

mixing a crystalline form of an active agent with a solvent;

adding a complexing agent and a co-solvent to the mixture; and

removing the solvent from the mixture so as to obtain the active agent in solid amorphous form.

21. The method of claim 20, wherein the active agent is paroxetine.

22. The method of claim 20, wherein the active agent is paroxetine hydrochloride.

23. The method of claim 20, wherein the active agent is spironolactone.

24. The method of claim 20, wherein the active agent is etodolac.

25. The method of claim 20, wherein the active agent is diclofenac.

26. The method of claim 20, wherein the active agent is a sodium or potassium salt of diclofenac.

27. The method of claim 20, wherein the solvent is an organic and volatile substance or water.

28. The method of claim 20, wherein the solvent is selected from the group consisting of ethanol, methanol, acetone, methylene chloride and a combination thereof.

29. The method of claim 20, wherein the solvent is ethanol.

30. The method of claim 20, wherein the complexing agent is selected from the group consisting of crospovidone, povidone, cyclodextrin and a combination thereof.

31. The method of claim 20, wherein the complexing agent is crospovidone.

32. The method of claim 20, wherein the non-volatile co-solvent is compatible with the active agent and miscible with the solvent.

33. The method of claim 20, wherein the non-volatile co-solvent is polyethylene glycol.

34. The method of claim 20, wherein the non-volatile co-solvent is polyethylene glycol 300.

35. The pharmaceutical composition produced by the method of claim 20.

36. A method for producing a pharmaceutical composition which comprises paroxetine hydrochloride that is maintained in a solid amorphous form, comprising:

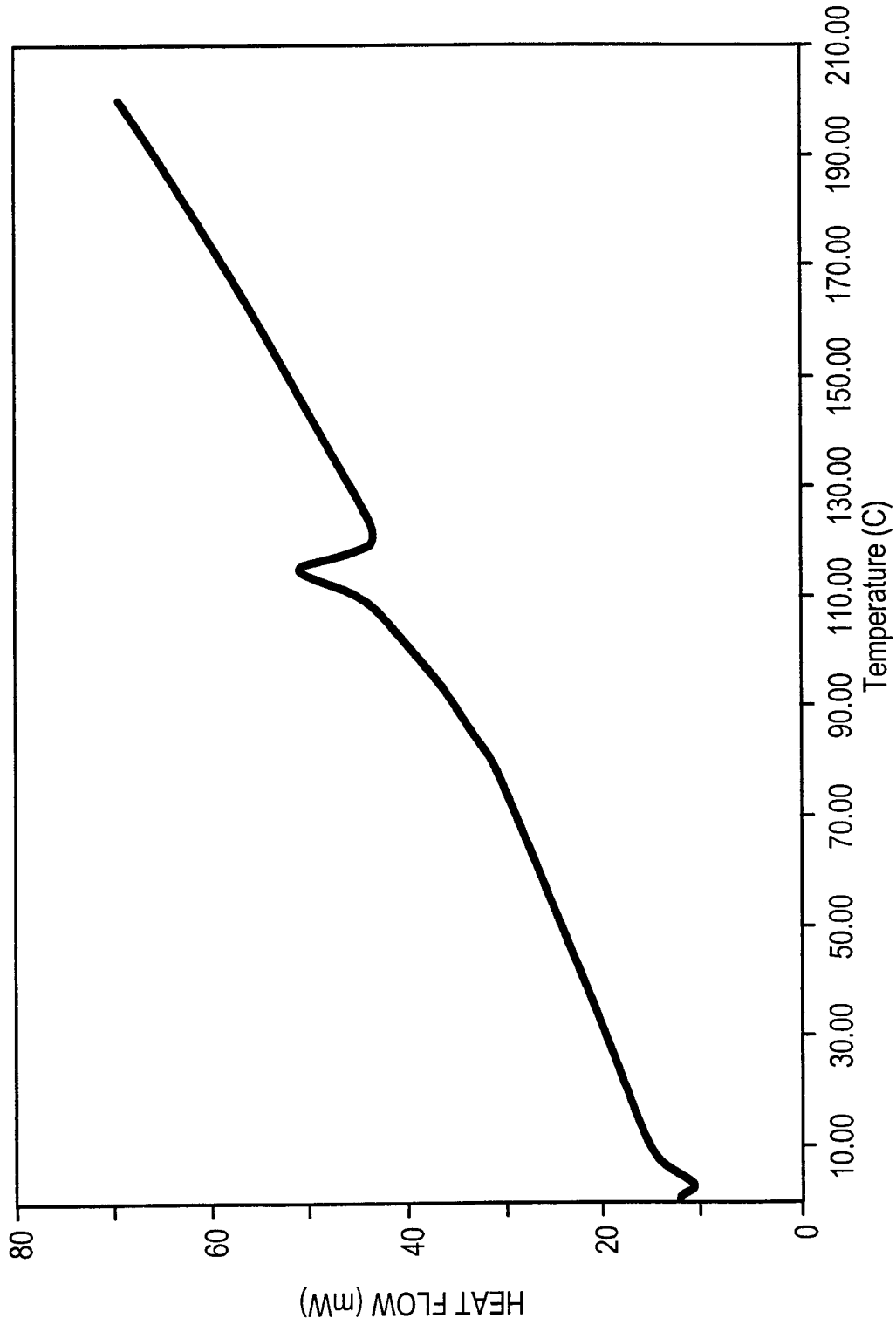
mixing a crystalline form of paroxetine hydrochloride with ethanol;

adding a complexing agent selected from the group consisting of crospovidone, povidone, cyclodextrin and a combination thereof, and polyethylene glycol 300 to the mixture; and

removing the ethanol from the mixture so as to obtain the paroxetine hydrochloride in solid amorphous form.

37. The pharmaceutical composition produced by the method of claim 36.

FIG. 1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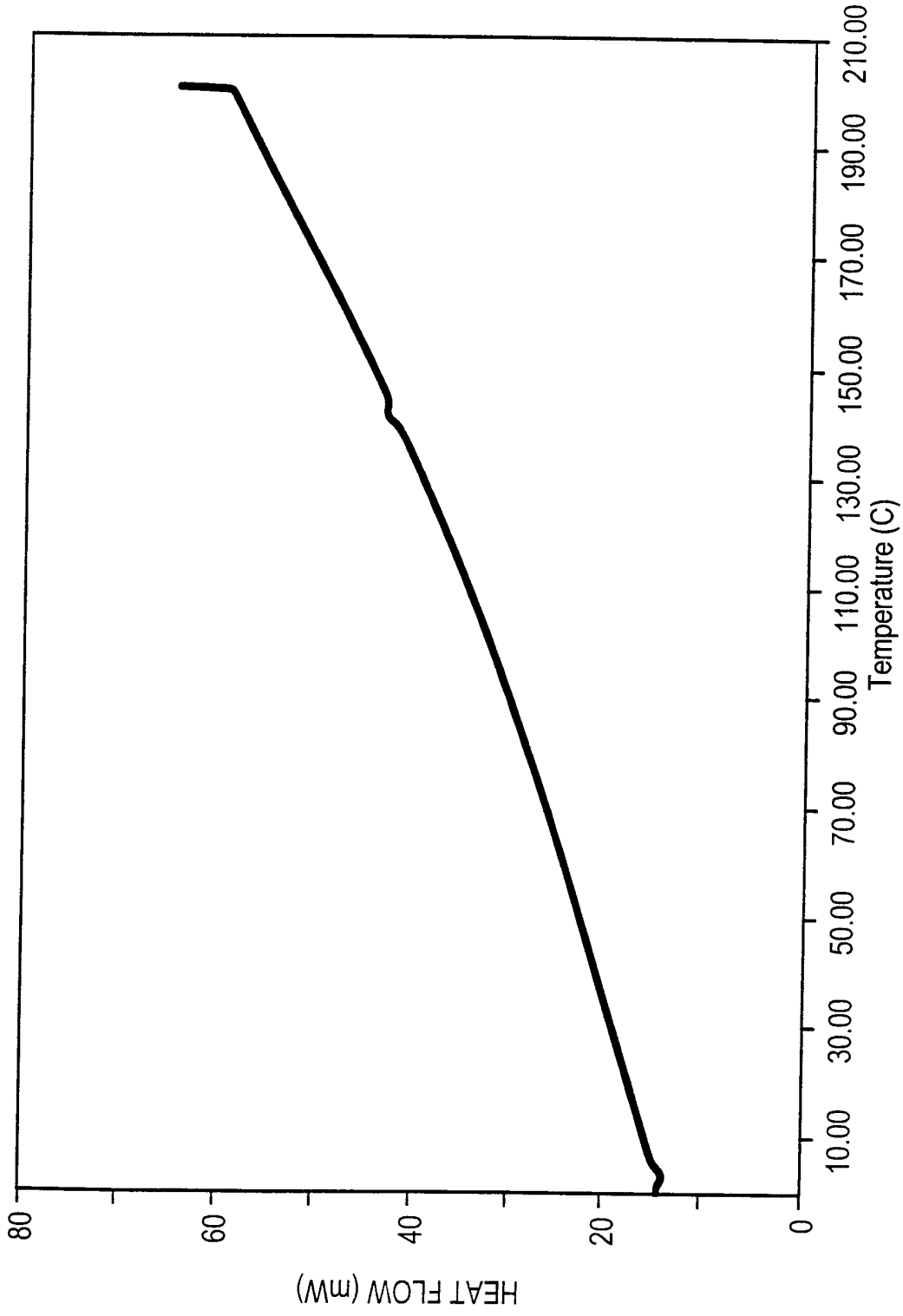
Temperature (C)

FIG. 2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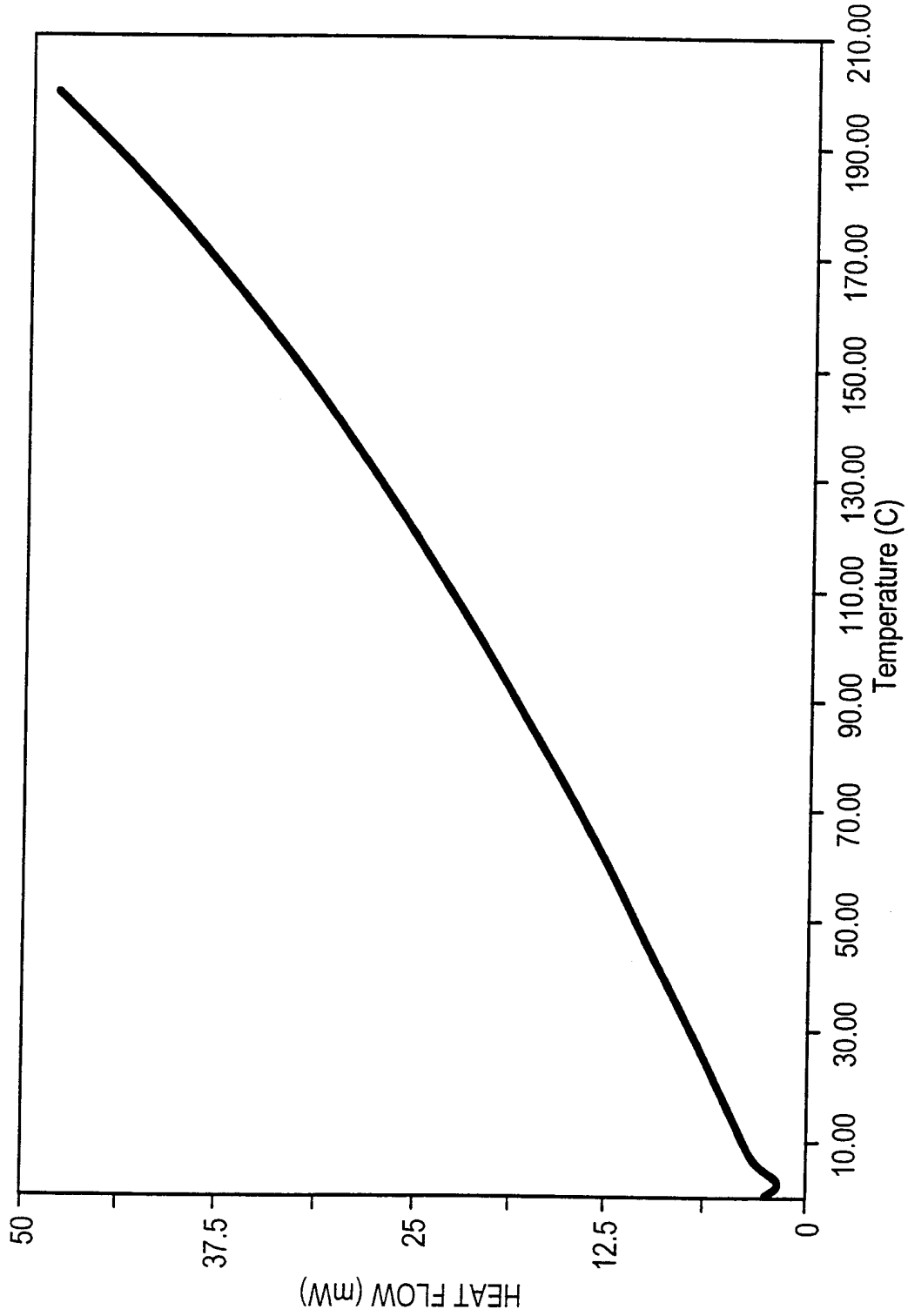
Temperature (C)

FIG. 3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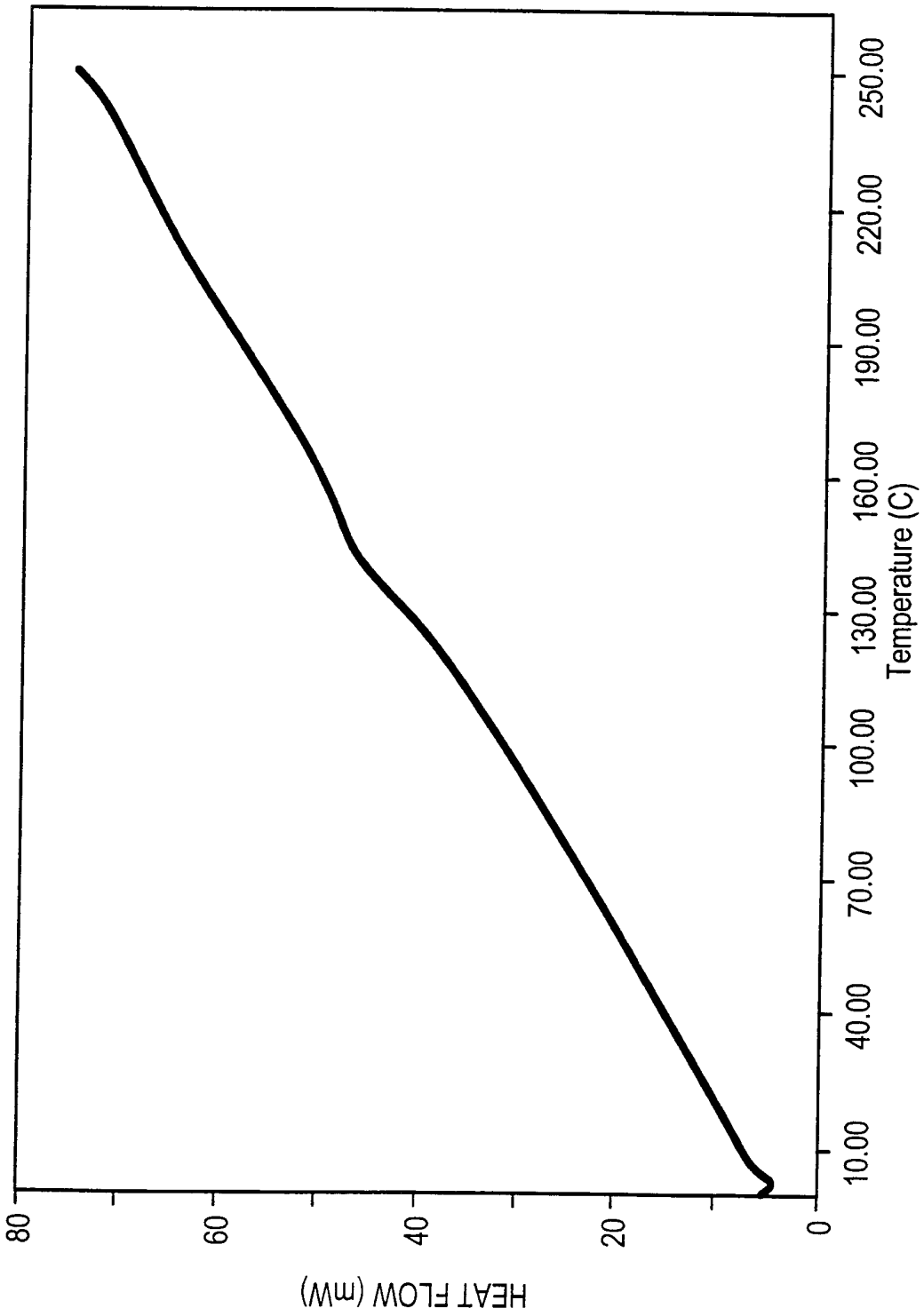
Temperature (C)

FIG. 4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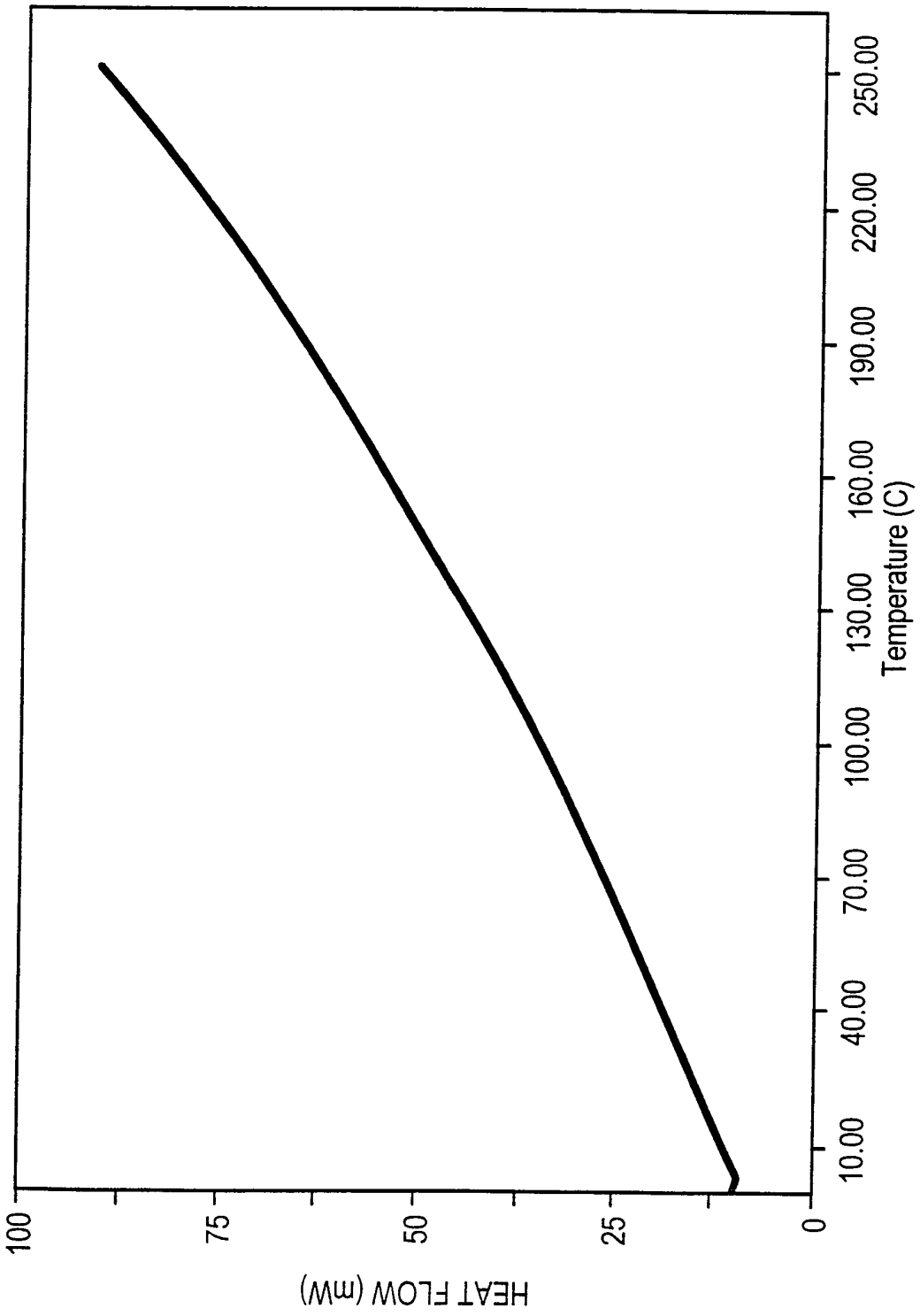
Temperature (C)

FIG. 5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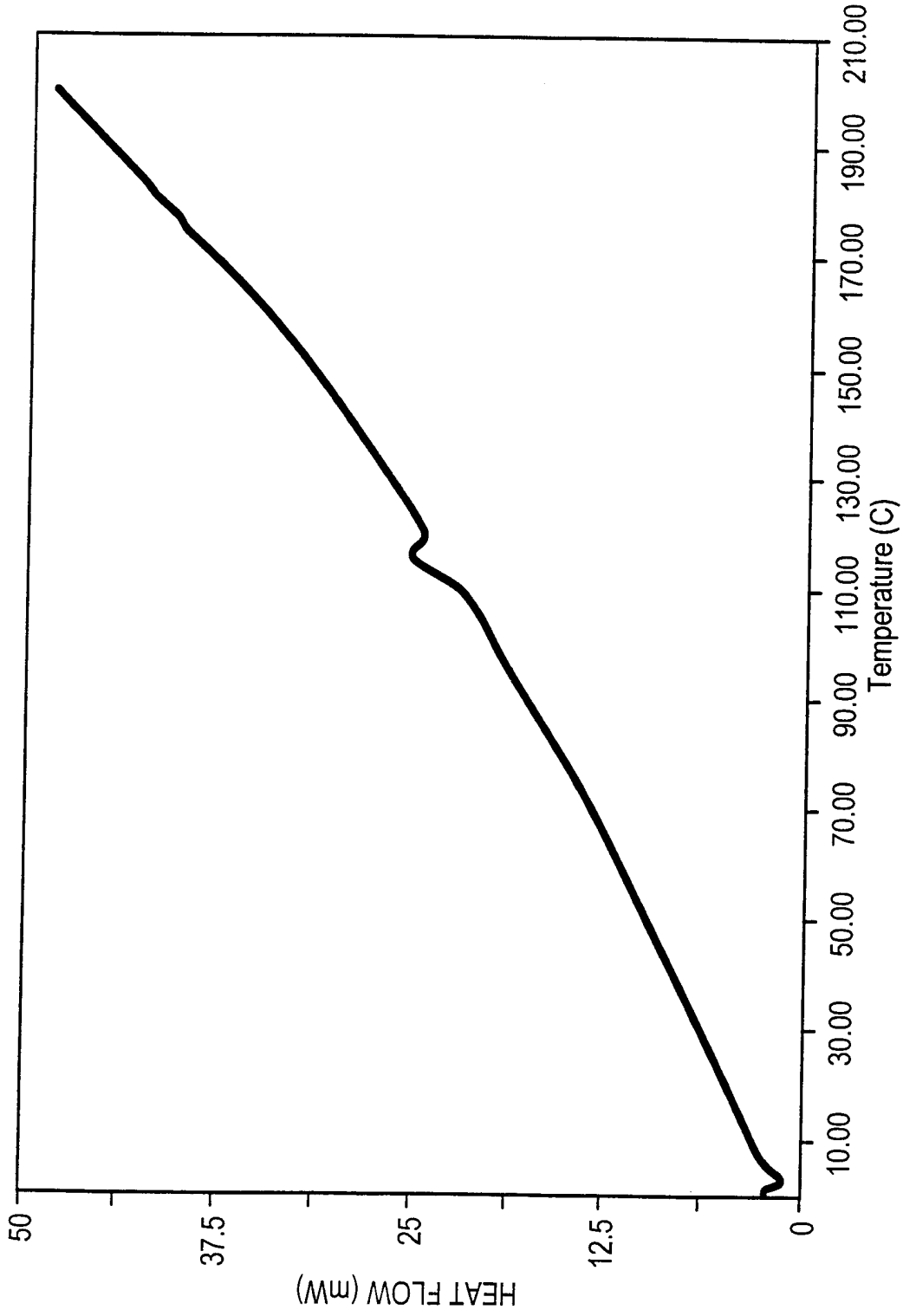
Temperature (C)

FIG. 6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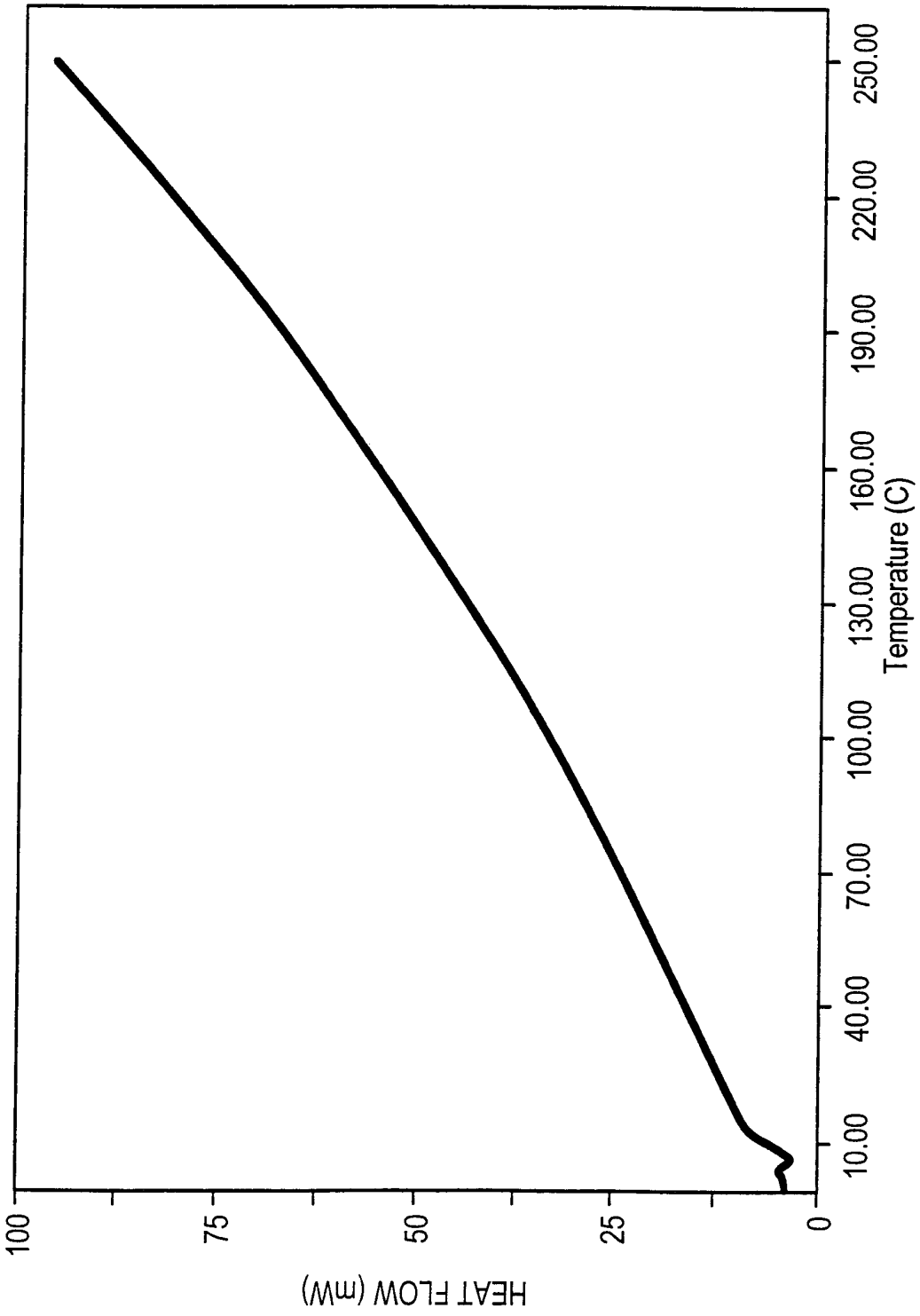
Temperature (C)

FIG. 7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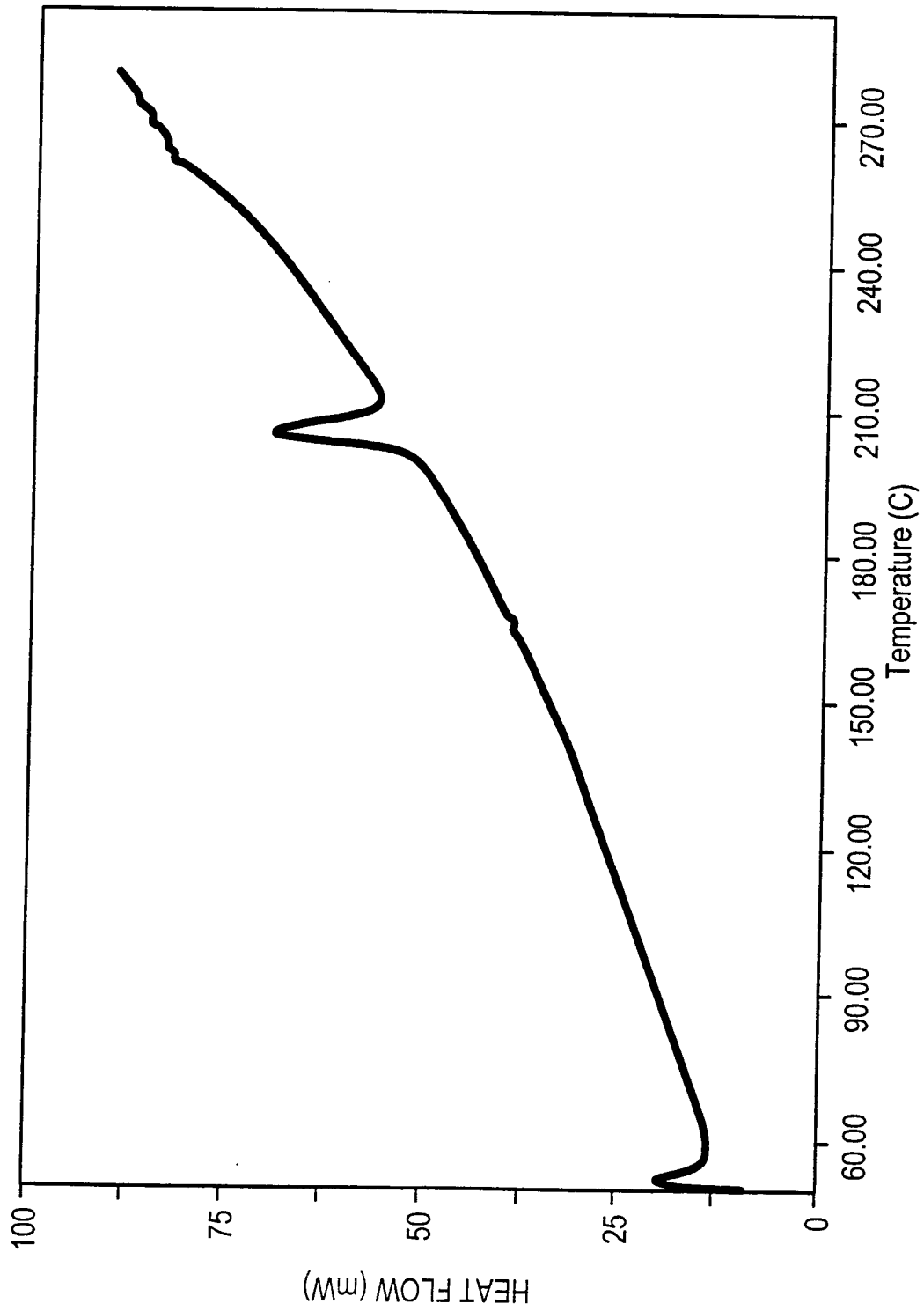
Temperature (C)

FIG. 8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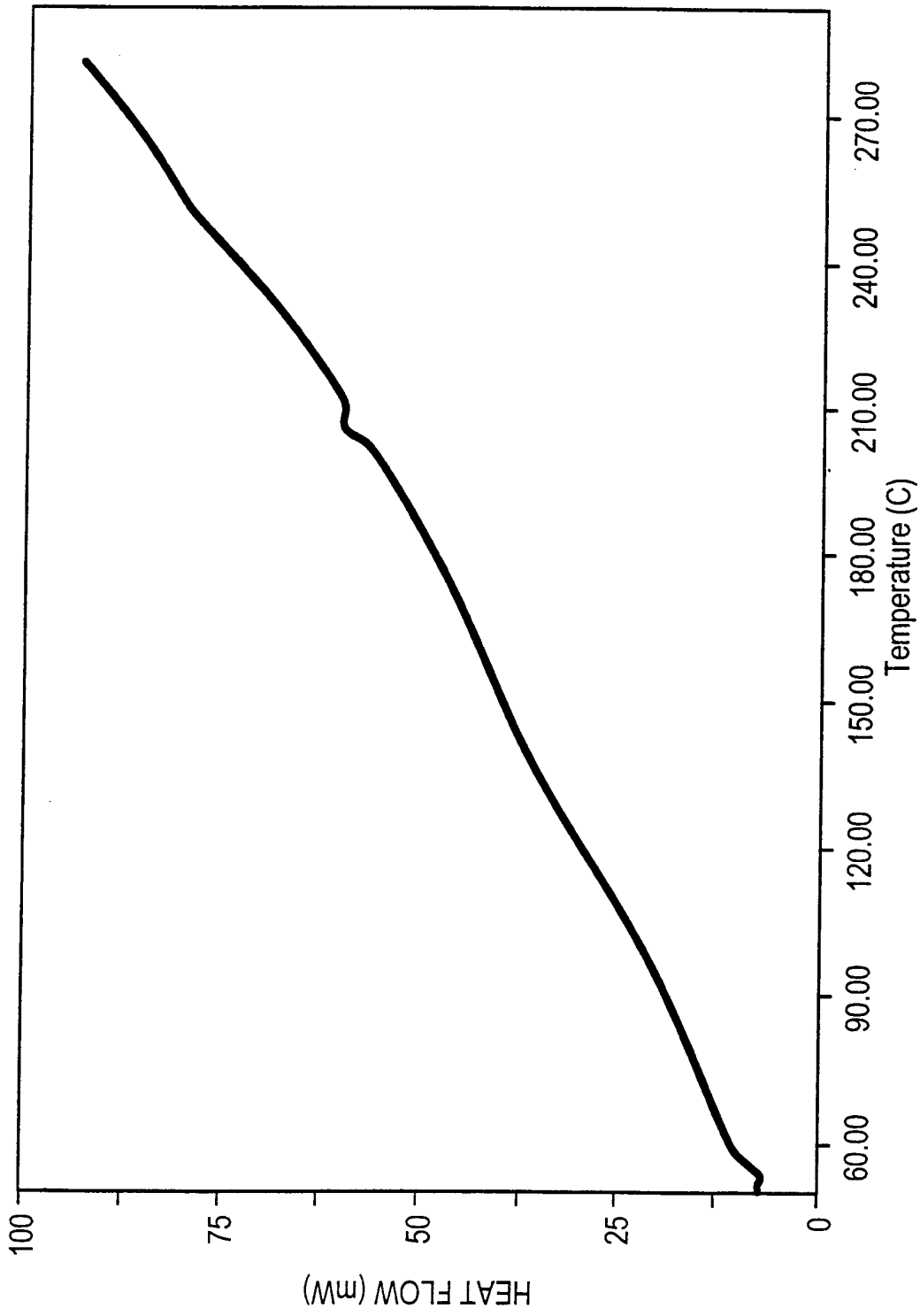
Temperature (C)

FIG. 9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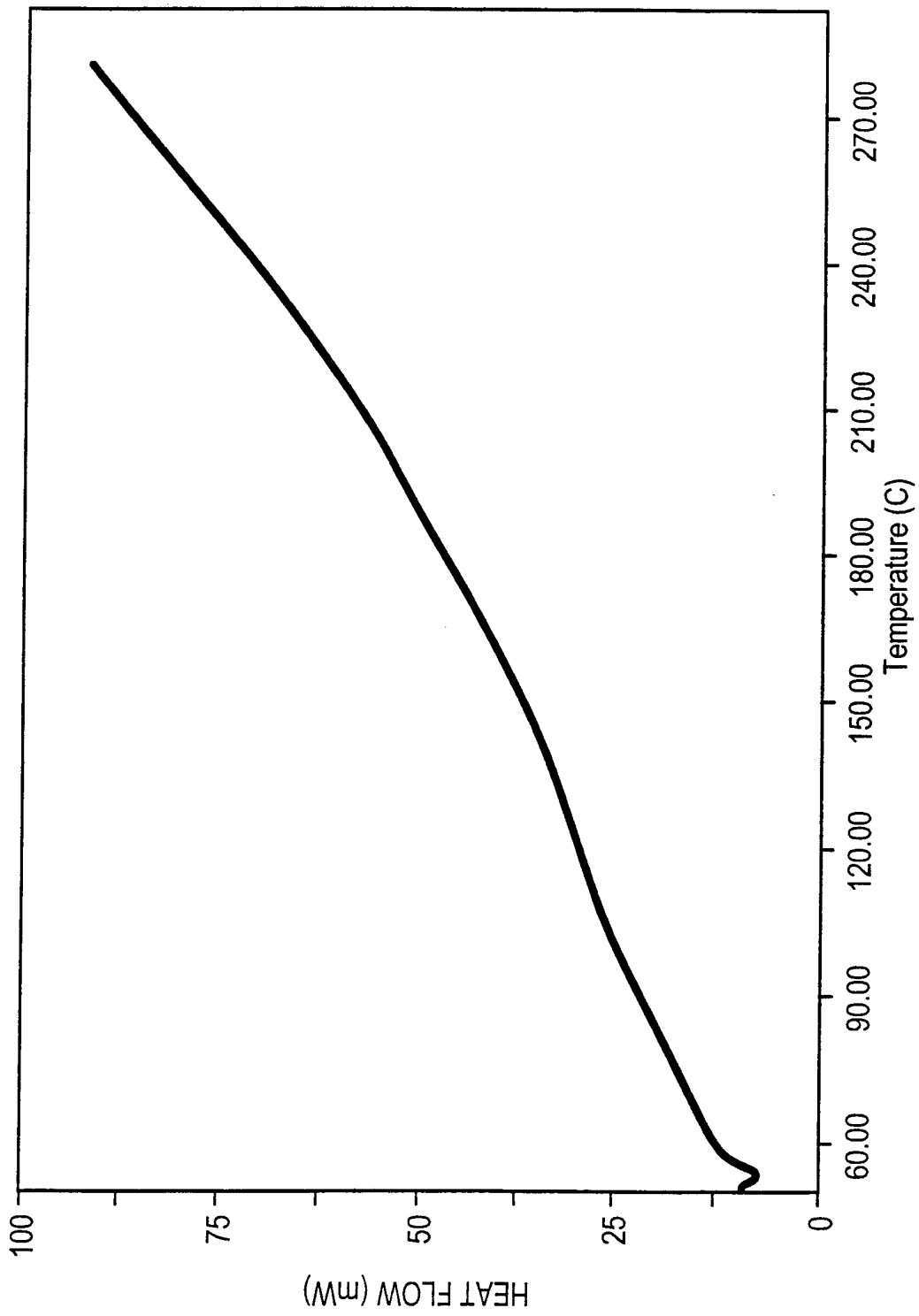
Temperature (C)

FIG. 10


HEAT FLOW (mW)
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Temperature (C)

FIG. 11

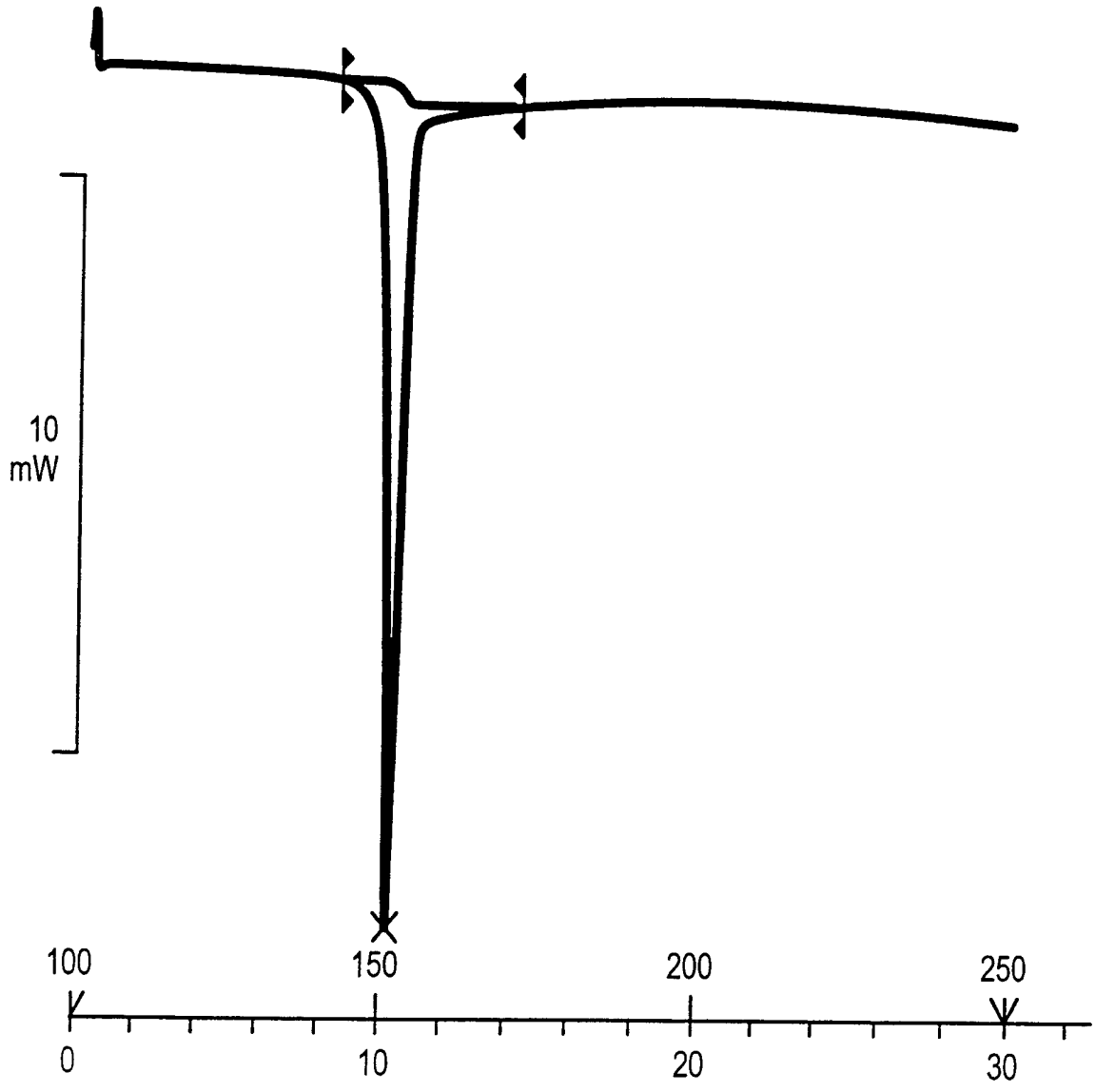


FIG. 12

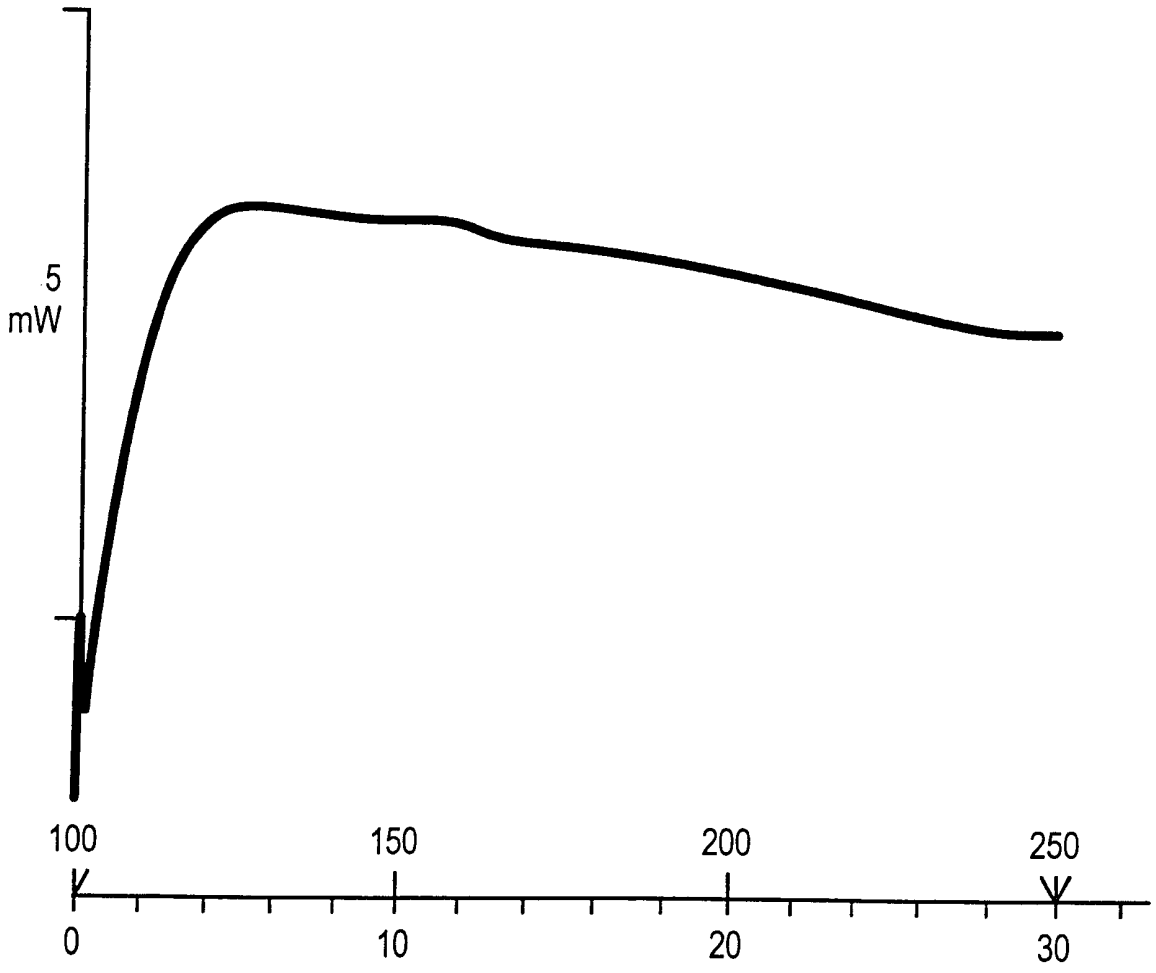


FIG. 13

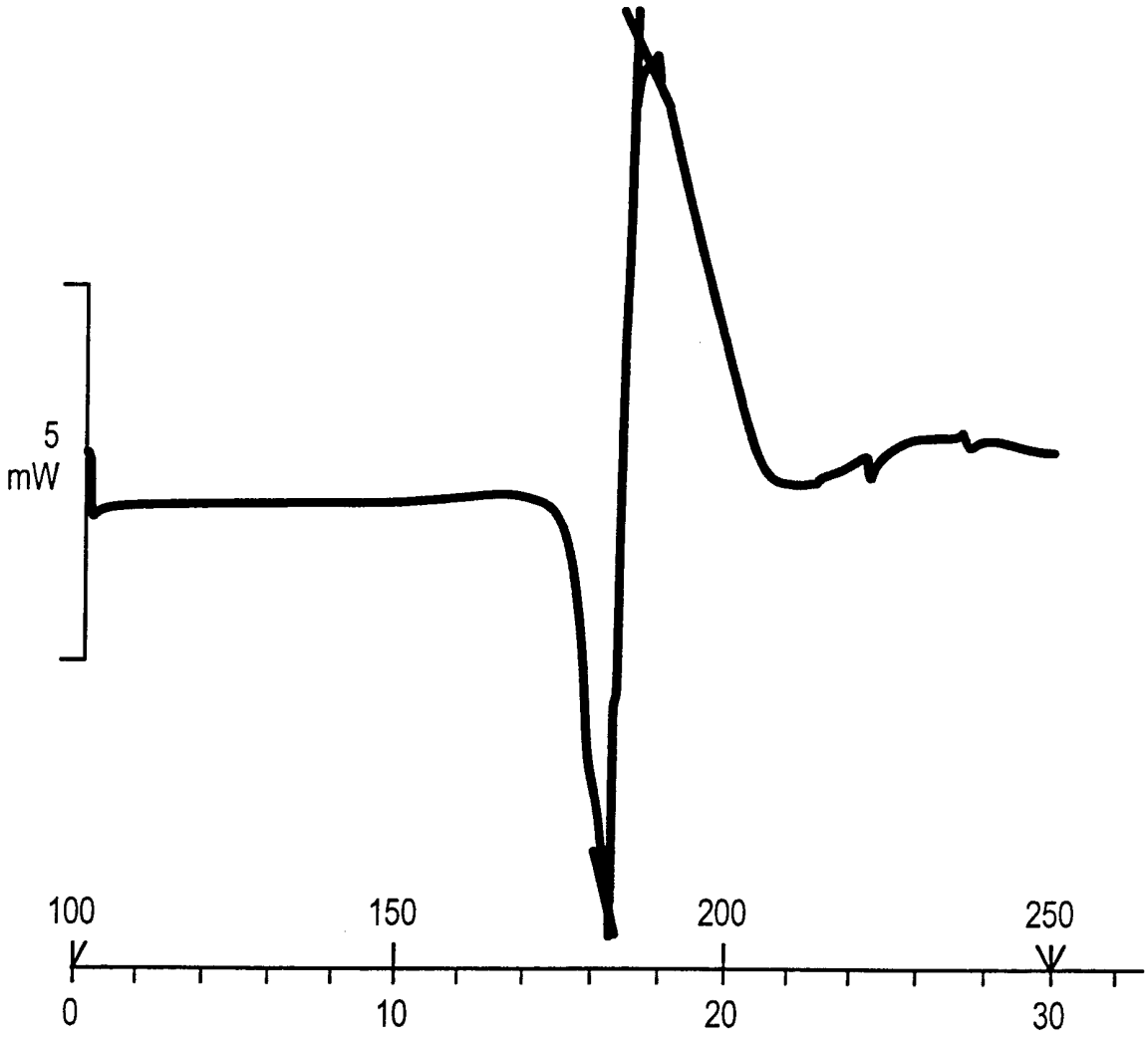
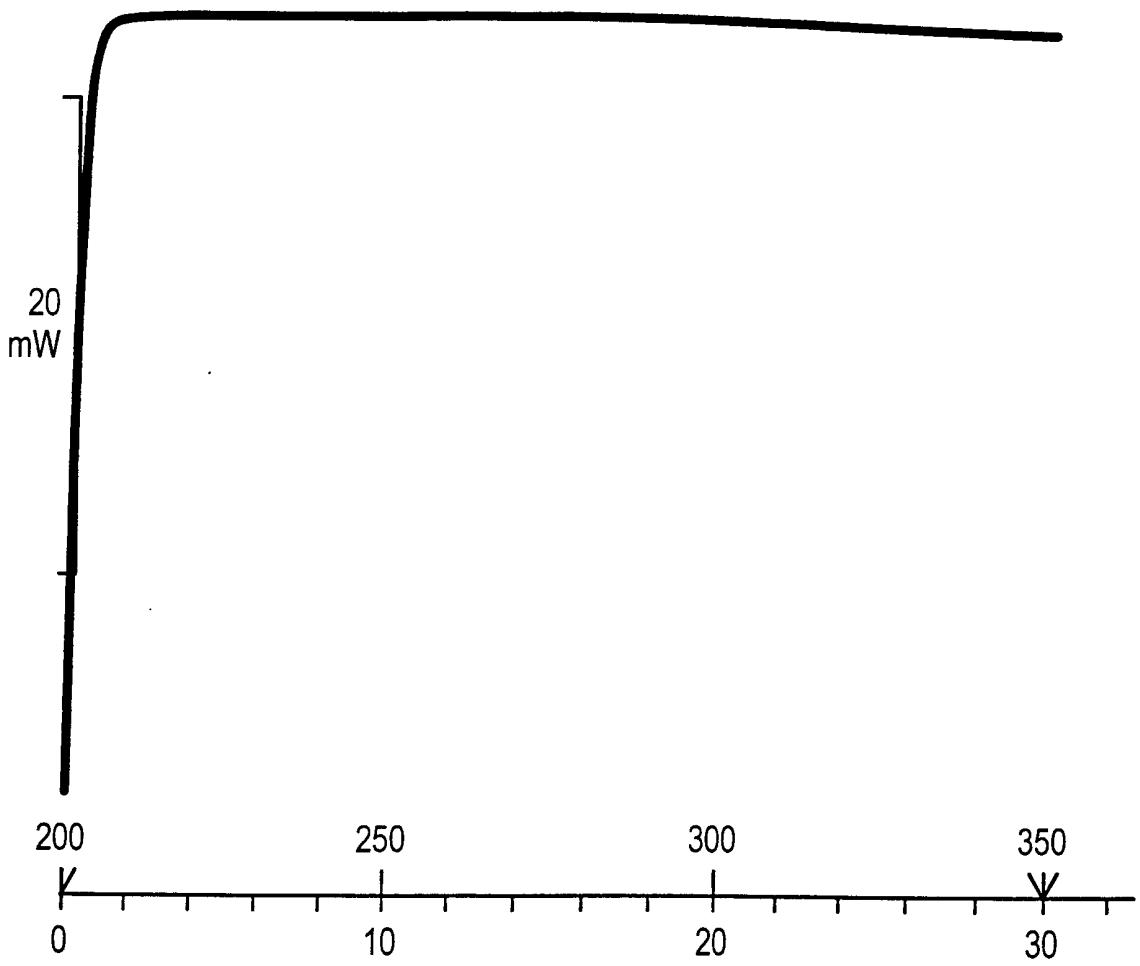


FIG. 14



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/14049

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 9/20, 9/14, 9/16, 9/50
US CL : 424/464, 486, 489, 497

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/464, 486, 489, 497

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,275,824 A (CARLI et al.) 04 January 1994, See entire document.	1-37
Y	US 5,399,584 A (ARES et al.) 21 March 1995, See entire document.	1-37
Y	US 5,788,987 A (BUSETTI et al.) 04 August 1998, See entire document.	1-37
Y,P	US 5,993,860 A (KUHRTS et al.) 30 November 1999, See entire document.	1-37
Y,P	US 6,066,643 A (PERRY) 23 May 2000, See entire document.	1-37

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
21 JULY 2000

Date of mailing of the international search report
28 AUG 2000

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Form PCT/ISA/210 (second sheet) (July 1998)★