(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 February 2005 (10.02.2005)

PCT

(10) International Publication Number
WO 2005/011666 A1

(51) International Patent Classification[7]: A61K 31/195, 9/20, A61P 25/08

(21) International Application Number: PCT/IB2004/051408

(22) International Filing Date: 5 August 2004 (05.08.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
968/DEL/2003 5 August 2003 (05.08.2003) IN

(71) Applicant *(for all designated States except US)*: **RANBAXY LABORATORIES LIMITED** [IN/IN]; 19, Nehru Place, New Delhi, Delhi 110019 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CHAWLA, Manish** [IN/IN]; 106, Lal Jyoti Apartments Sector - 9, Plot - 16, Rohini, Delhi 110085 (IN). **RAGHUVANSHI, Rajeev, Singh** [IN/IN]; Flat No. 8131 Block: D-8 Vasant Kunj, New Delhi, Delhi 110070 (IN). **RAMPAL, Ashok** [IN/IN]; 14 Sewa Nagar Ram Tirath Road, Amritsar, Punjab 143001 (IN).

(74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o DESHMUKH, Jay R., 600 College Road East, Suite 2100, Princeton, New Jersey 08540 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, 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 receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/011666 A1

(54) Title: STABLE SUSTAINED RELEASE ORAL DOSAGE FORM OF GABAPENTIN

(57) Abstract: The present invention relates to stable sustained release oral dosage form of gabapentin and methods of making these dosage forms. The stable sustained release tablet is prepared from granules. The granules include gabapentin; one or more hydrophilic rate-controlling polymers selected from the group consisting of hydroxypropylcellulose, polyvinylpyrrolidone and its derivatives, and polysaccharide gum; and, optionally, one or more pharmaceutical excipients.

Description

STABLE SUSTAINED RELEASE ORAL DOSAGE FORM OF GABAPENTIN

Technical Field

[1] The present invention relates to stable sustained release oral dosage forms of gabapentin and methods for making these dosage forms.

Background Art

[2] When a drug dosage form is designed for human consumption, it is desired that the drug show its maximum therapeutic efficacy with minimum side effects. Some of the side effects inherent in the drug can only be minimized if not eliminated, by adjusting the dosing regimen or modifying the bioavailability parameters through designing of dosage forms with sustained release of the drug. But if the drug is susceptible to degradation and forms toxic byproducts over time as such, or due to incompatibility with the excipients present in the dosage form, its consumption can be detrimental to the health of the patient. Various pharmacopeias require that dosage forms be free of these toxic degradation products or, if present, should be within safe permissible limits.

[3] Gabapentin (1-(aminomethyl)cyclohexaneacetic acid) is a #-amino acid analogue effective in the treatment of epilepsy. Gabapentin is indicated as an adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy. Gabapentin has also been approved for neuropathic pain in some countries.

[4] Gabapentin has been reported to convert to a toxic lactam compound during preparation and storage. This lactam formation is also seen in formulations containing gabapentin. The lactam formation in formulation during storage is apparently a result of the catalytic effects of the excipients used. The lactam has toxicity, which exceeds that of gabapentin itself. The lethal dose (LD_{50}) of gabapentin in mice has been reported to be 8,000 mg/kg while that of the corresponding lactam is 300 mg/kg. Consequently, these impurities and the potential formation of such decomposition products during storage of pharmaceutical compositions must be reduced to a minimum for reasons of safety.

[5] Considering the instability of gabapentin in the dosage form and its short half life, it would be advantageous to design a sustained release dosage form of gabapentin which is stable on storage, has low lactam content and provides therapeutically effective plasma levels of gabapentin over a prolonged period. These stable sustained release dosage forms of gabapentin would not only provide a safe mode of gabapentin therapy but also would provide other benefits, such as maintaining steady plasma levels of gabapentin and the possibility of reducing the total daily dose and frequency of dosing to once or twice a day.

[6] U.S. Patent No. 6,054,482 provides a list of adjuvants which are purported to have no noticeable influence on the stability of gabapentin. This list includes, among others, hydroxypropylmethylcellulose. Further, U.S. Patent Application no. 2003/0100611 discloses gastric retained dosage forms of gabapentin that contain hydrophilic polymers. Exemplary polymers disclosed include high viscosity or high molecular weight hydroxypropylmethylcellulose. As such, the prior art appears to teach that hydroxypropyl methylcellulose is compatible with gabapentin.

Disclosure

[7] Summary of the Invention

[8] In one general aspect there is provided a stable sustained release tablet prepared from granules. The granules include gabapentin; one or more hydrophilic rate-controlling polymers selected from the group consisting of hydroxypropylcellulose, polyvinylpyrrolidone and its derivatives, and polysaccharide gum; and, optionally, one or more pharmaceutical excipients.

[9] Embodiments of the sustained release tablet may include one or more of the following features. For example, the lactam content of the tablet may not exceed 0.6% by weight of gabapentin when stored for three months at 40°C and 75% relative humidity. The tablet may provide therapeutically effective plasma levels of gabapentin for up to about 24 hours. The sustained release tablet may have a dissolution profile measured in a USP type II dissolution apparatus, at 50 rpm, at a temperature of 37±0.5°C in 900ml of 0.06N hydrochloric acid of at least 90% of the gabapentin being released in a time between 4 hours and 12 hours. More particularly, at least 90% of the gabapentin may be released in a time between 8 hours and 12 hours.

[10] The gabapentin may make up from about 100 mg to about 1,200mg by weight of the tablet.

[11] The hydroxypropylcellulose may have a viscosity of between about 7 cps and about 30,000 cps. In particular, the hydroxypropylcellulose may have a viscosity of between about 4,000 cps and about 15,000 cps.

[12] The polyvinylpyrrolidone derivative may be selected from crospovidone, copolyvidone and physical mixtures of polyvinylpyrrolidone and polyvinylacetate. The polysaccharide gum may be selected from the group consisting of guar gum, gum arabic, xanthan gum, locust bean gum, gum karaya and gum tragacanth or combinations thereof.

[13] The pharmaceutical excipients may be selected from diluents, binders, lubricants and glidants. The sustained release tablet may be formulated such that the granules do not contain hydroxymethyl propylcellulose. The sustained release tablet may further include one or more pharmaceutical excipients mixed with the granules.

[14] In another general aspect there is provided a process for the preparation of a stable sustained release tablet. The process includes:

[15] granulating a mixture of gabapentin and one or more hydrophilic rate-controlling

polymers selected from the group consisting of hydroxypropylcellulose; polyvinylpyrrolidone and its derivatives, and polysaccharide gum or combinations thereof with a granulating liquid or a binder solution;

[16] drying the granules;

[17] mixing the dried granules with one or more pharmaceutical excipients to form a blend; and

[18] compressing the blend into a tablet.

[19] Embodiments of the process may include one or more of the following features. For example, the lactam content of the tablet may not exceed 0.6% by weight of gabapentin when stored for three months at 40°C and 75% relative humidity. The tablet may provide therapeutically effective plasma levels of gabapentin for up to about 24 hours. The sustained release tablet may have a dissolution profile measured in a USP type II dissolution apparatus, at 50 rpm, at a temperature of 37±0.5°C in 900ml of 0.06N hydrochloric acid of at least 90% of the gabapentin being released in a time between 4 hours and 12 hours. More particularly, at least 90% of the gabapentin may be released in a time between 8 hours and 12 hours.

[20] The gabapentin may make up between about 100 mg and about 1,200 mg by weight of the tablet. The hydroxypropylcellulose may have a viscosity of between about 7 cps and about 30,000 cps. In particular, the hydroxypropylcellulose may have a viscosity of between about 4,000 cps and about 15,000 cps.

[21] The polyvinylpyrrolidone derivative is selected from crospovidone, copolyvidone and physical mixtures of polyvinylpyrrolidone and polyvinylacetate. The polysaccharide gum is selected from the group consisting of guar gum, gum arabic, xanthan gum, locust bean gum, gum karaya and gum tragacanth or combinations thereof. The other pharmaceutical excipients are selected from diluents, binders, lubricants and glidant.

[22] The process may further include granulating one or more pharmaceutical excipients with the mixture of gabapentin and one or more hydrophilic rate-controlling polymers.

[23] In another general aspect, there is provided a method of treating a medical condition. The method includes providing an oral pharmaceutical sustained release tablet prepared from granules comprising gabapentin, one or more hydrophilic rate controlling polymers selected from the group consisting of hydroxypropylcellulose, polyvinylpyrrolidone and its derivatives, and polysaccharide gum and optionally one or more pharmaceutical excipients.

[24] Embodiments of the method of treating may include one or more of the following features or those described above. For example, the medical condition may be one or both of epilepsy and neuropathic pain.

[25] The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

[26] Detailed Description of the Invention

[27] Based on the teaching of the prior art disclosures described above, we prepared gabapentin tablets with high viscosity and high molecular weight hydroxypropyl methylcellulose. However, contrary to the prior art disclosures, these tablets showed an increase in lactam content on storage (see Examples 5 and 6 and Table 4, herein). Because of the finding that high molecular weight or high viscosity hydroxypropyl methylcellulose actually increases the lactam content, we had to carry out laborious investigations to establish which alkyl substituted cellulose material or hydrophilic polymer is actually compatible with gabapentin.

[28] Surprisingly, as a result of these efforts we discovered that stable sustained release gabapentin tablets can be prepared using hydrophilic polymers selected from the group consisting of hydroxypropylcellulose, polyvinylpyrrolidone and its derivatives, and polysaccharide gums and one or more pharmaceutically acceptable excipients. When these sustained release tablets were kept for three months at 40 ° C and 75% relative humidity, the lactam content did not exceed 0.6% by weight of gabapentin. These sustained release tablets of gabapentin are believed to be capable of maintaining plasma levels of gabapentin in a therapeutic range over an extended time period for up to about 24 hours. This can be accomplished, for example, by varying the concentration of polymers within the granules and possibly outside the granules.

[29] The stability conditions as defined herein include tolerance of ± 2 ° C in temperature and a tolerance of ± 5% in relative humidity.

[30] Gabapentin may be present as a free base, hydrated form such as monohydrate or any other pharmaceutically acceptable salts thereof. Gabapentin may comprise from about 100 mg to about 1200 mg by weight of the tablet.

[31] Hydroxypropylcellulose, as used herein, can be of different viscosity grades such as sold by Aqualon under the brand name of Klucel® and also by Nippon Soda Co. Ltd, Japan. Suitable grades are those having viscosity of from about 7 to about 30,000 cps. Especially suitable among these hydroxypropylcelluloses are those having viscosity of 4000 to about 30,000 cps. Typically the amount of hydroxypropylcellulose can be from about 3% to about 40%, particularly from about 5% to about 30% and more particularly from about 5% to about 25% by weight of granules.

[32] Polyvinylpyrrolidone or PVP refers to a polymer containing N-vinylpyrrolidone as the monomeric unit and is known to the pharmaceutical industry under a variety of designations including povidone, polyvidone, polyvidonum, polyvidonum soluble, and poly(1-vinyl-2-pyrrolidone). Cross-linked polyvinylpyrrolidone, known as crospovidone available as Kollidon CL and Kollidon CL-M is also included. The polyvinylpyrrolidone derivatives include among others the copolymer of N-vinyl-2-pyrrolidone and vinyl acetate which is known as copolyvidon, copolyvidone, and copolyvidonum. Physical mixtures of polyvinylpyrrolidone and polyvinyl acetate are also included. These mixtures can be in a ratio such as, but not limited to, 20:80

(PVP: polyvinylacetate) like Kollidon SR. It is apparent that other derivatives of polyvinylpyrrolidone known to those skilled in the art can also be used. Polyvinylpyrrolidone is available in a wide range of molecular weights. Particularly suitable are grades having molecular weights between about 8,000 to about 1,300,000 such as Plasdone K-90, Plasdone K-90D. Typically the amount of polyvinylpyrrolidone and its derivatives can be from about 3% to about 40%, particularly from about 3% to about 30% by weight of granules.

[33] Polysaccharide gums may be selected from the group consisting of guar gum, gum arabic, xanthan gum, locust bean gum, gum karaya and gum tragacanth. Particularly suitable is guar gum. Typically the amount of polysaccharide gum can be from about 3% to about 80%, particularly from about 3% to about 70% and more particularly from about 3% to about 60% by weight of the granules.

[34] The other pharmaceutical excipients are selected from the group consisting of diluents, binders, lubricants and glidants. Suitable diluents include powdered sugar, calcium phosphate, calcium sulfate, microcrystalline cellulose, lactose, mannitol, kaolin, dry starch, sorbitol, etc. Suitable binders include polyvinylpyrrolidone and its derivatives; xanthan gum, guar gum; cellulose ethers such as carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose (extragranularly only, not intragranularly), hydroxypropyl cellulose, ethyl cellulose; gelatin, starch and its derivatives. The granulating liquid can be, but is not limited to, water, ethanol, isopropyl alcohol, acetone, dichloromethane and the like. Alternatively, the binder can be dissolved in the granulating liquid and used as a solution. Lubricants can be talc, stearic acid, vegetable oil, calcium stearate, zinc stearate and magnesium stearate and glidants include talc, silicon dioxide and cornstarch.

[35] In one embodiment, stable gabapentin sustained release tablets may be prepared by

[36]

1. Blending gabapentin with hydrophilic rate-controlling polymer(s) like hydroxypropylcellulose, polyvinylpyrrolidone and its derivatives or polysaccharide gum and other pharmaceutical excipients (but not HPMC) in a mixer.
2. Granulating the blend of step (1) with a granulating liquid or a binder solution.
3. Drying and sizing the granules.
4. Mixing the sized granules with other pharmaceutical excipients and compressing into tablet.

[37] In another embodiment, stable gabapentin sustained release tablets may be prepared by following the steps of

[38]

1. Blending gabapentin with a portion of hydroxypropylcellulose in a mixer.
2. Granulating the blend of step (1) with a solution of remaining portion of hy-

droxypropylcellulose in a granulating liquid.

3. Drying and sizing the granules.
4. Mixing the sized granules with other pharmaceutical excipients and compressing into tablet.

[39] Tablets can additionally be coated with non-rate-controlling polymer(s) compositions like Opadry® sold by Colorcon to impart aesthetic appeal. Such a coating may comprise about 2% by weight of the tablet.

[40] Stable gabapentin sustained release tablets and process for the preparation thereof described herein is further illustrated by the following examples but these should not be construed as limiting the scope of the invention.

[41] **Preformulation studies**

[42] In an excipient compatibility study, the compatibility of gabapentin with hydroxypropylcellulose, polyvinylpyrrolidone, copolyvidone, guar gum and hydroxypropyl methylcellulose among other pharmaceutical excipients was determined. Gabapentin was mixed with these polymers and the mixture was granulated with purified water, the granules were dried, sized and compressed to form tablets. The tablets were then kept for three months at 40 ° C and 75% relative humidity in sealed HDPE bottles. The stability data is given below in Table 1.

[43] **Table 1 Stability data of preformulation studies**

[44]

Excipient / (w/w% of granules)	**Lactam Content (% w/w)**	
	Initial	**3 Months/ 40 ° C/75%RH**
Gabapentin (100%)	0.080	0.077
Gabapentin + Hydroxypropylcellulose (12.4%)	0.024	0.268
Gabapentin + Polyvinylpyrrolidone (5.2%)	0.049	0.202
Gabapentin + Guar gum (12%)	0.014	0.302
Gabapentin + Hydroxypropylmethylcellulose (10.9%)	0.083	0.816
Gabapentin +	0.034*	0.053*

Copolyvidone (2%)		

[45] * 2 Months at 40 ° C/75% RH

[46] **EXAMPLES 1 - 4**

[47]

Ingredients	**Quantity (mg)**			
	Example 1	**Example 2**	**Example 3**	**Example 4**
Gabapentin	900	900	900	900
Hydroxypro	120	100	100	265
pylcellulose	60.5	81	93	15.5
Mannitol	15	12	12	15
Poloxamer	12	12	--	12
Copolyvidon	20	15	15	20
e	22.5	15	15	22.5
Magnesium stearate				
Talc				
Total	**1150**	**1135**	**1135**	**1250**

[48] **General Procedure:**

[49] Gabapentin was mixed with a portion of hydroxypropylcellulose and granulated with remaining portion of hydroxypropylcellulose dissolved in purified water. The granules were dried and sized, mixed with mannitol, copolyvidone (Examples 1, 2 and 4), poloxamer, magnesium stearate and talc and compressed to form a tablet. The tablets were then kept for three months at 40 ° C and 75% relative humidity in sealed HDPE bottles. The stability data is given in Table 2 and shows that the formulations are stable.

[50] **Table 2 Stability data of the tablets of Examples 1-4 when stored for three months at 40 ° C and 75% relative humidity (RH).**

[51]

	Lactam Content (% w/w)			
	Example 1	**Example 2**	**Example 3**	**Example 4**
Initial	0.034	0.035	0.032	0.039
3 Month/40 ° C/ 75% RH	0.337	0.249	0.236	0.514

[52] The dissolution profile of tablets of Examples 1-4 measured in a USP type II dissolution apparatus, at 50 rpm, at a temperature of 37±0.5 ° C in 900 ml of 0.06N hydrochloric acid is given below in Table 3. These profiles show complete release of the

drug over a time ranging between 4 hours and 12 hours.

[53] **Table 3 Dissolution profiles of tablets of examples 1- 4 measured in a USP type II dissolution apparatus, at 50 rpm, at a temperature of 37±0.5 ° C in 900ml of 0.06N hydrochloric acid**

[54]

Time (Hrs.)	% Drug Release			
	Example 1	Example 2	Example 3	Example 4
0.5	18	21	22	--
1	29	44	44	24
2	47	73	74	36
3	--	92	93	--
4	75	98	99	52
6	95			65
8	104			77
10				87
12				93

[55] **EXAMPLES 5 and 6**

[56]

Ingredients	Quantity (mg)	
	Example 5	Example 6
Gabapentin	900	900
Hydroxypropyl methyl-	100	250
cellulose	81	76
Mannitol	12	12
Poloxamer	12	12
Copolyvidone	15	10
Magnesium stearate	15	10
Talc		
Total	**1135**	**1270**

[57] **Procedure**

[58] Gabapentin was mixed with a portion of hydroxypropylmethylcellulose and mannitol and granulated with the remaining portion of hydroxypropylmethylcellulose dissolved in purified water. The granules were dried and sized, mixed with copolyvidone, poloxamer, magnesium stearate and talc and compressed to form a tablet. These tablets were kept for 3 months at 40 ° C and 75% relative humidity in

sealed HDPE bottles. The stability data is given in Table 4.

[59] **Table 4 Stability data of tablets of example 5 when stored for three months at 40 ° C and 75% relative humidity (RH).**

[60]

	Lactam Content (% w/w)	
	Example 5	Example 6
Initial	0.021	0.141
3 Month/40 ° C/75% RH	1.038	2.184

[61] The data in Table 1 and 4 clearly indicate the incompatibility of Gabapentin with HPMC.

[62] While several particular forms of the inventions have been described, it will be apparent that various modifications and combinations of the inventions detailed in the text can be made without departing from the spirit and scope of the inventions. Accordingly, it is not intended that the inventions be limited, except as by the appended claims.

Claims

[1] A stable sustained release tablet prepared from granules, the granules comprising:

gabapentin;

one or more hydrophilic rate-controlling polymers selected from the group consisting of hydroxypropylcellulose, polyvinylpyrrolidone and its derivatives, and polysaccharide gum; and

optionally one or more pharmaceutical excipients.

[2] The sustained release tablet according to claim 1 wherein the lactam content of the tablet does not exceed 0.6% by weight of gabapentin when stored for three months at 40 ° C and 75% relative humidity.

[3] The sustained release tablet according to claim 1 wherein the tablet provides therapeutically effective plasma levels of gabapentin for up to about 24 hours.

[4] The sustained release tablet according to claim 1 wherein gabapentin comprises from about 100 mg to about 1,200 mg by weight of the tablet.

[5] The sustained release tablet according to claim 1 wherein the hydroxypropyl-cellulose has a viscosity of between about 7 cps and about 30,000 cps.

[6] The sustained release tablet according to claim 5 wherein the hydroxypropyl-cellulose has a viscosity of between about 4,000 cps and about 15,000 cps.

[7] The sustained release tablet according to claim 1 wherein the polyvinylpyrrolidone derivative is selected from crospovidone, copolyvidone and physical mixtures of polyvinylpyrrolidone and polyvinylacetate.

[8] The sustained release tablet according to claim 1 wherein the polysaccharide gum is selected from the group consisting of guar gum, gum arabic, xanthan gum, locust bean gum, gum karaya and gum tragacanth or a combinations thereof.

[9] The sustained release tablet according to claim 1 wherein the pharmaceutical excipients are selected from diluents, binders, lubricants and glidant.

[10] The sustained release tablet according to claim 1 wherein the granules do not contain hydroxypropyl methylcellulose.

[11] The sustained release tablet according to claim 1 wherein the tablet further comprises one or more pharmaceutical excipients mixed with the granules.

[12] The sustained release tablet according to claim 1 wherein the tablet has a dissolution profile measured in a USP type II dissolution apparatus, at 50 rpm, at a temperature of 37±0.5°C in 900ml of 0.06N hydrochloric acid of at least 90% of the gabapentin being released in a time between 4 hours and 12 hours.

[13] The sustained release tablet according to claim 12 wherein at least 90% of the gabapentin is released in a time between 8 hours and 12 hours.

[14] A process for the preparation of a stable sustained release tablet, the process comprising:

granulating a mixture of gabapentin and one or more hydrophilic rate-controlling polymers selected from the group consisting of hydroxypropyl-cellulose; polyvinylpyrrolidone and its derivatives, and polysaccharide gum or combinations thereof with a granulating liquid or a binder solution;
drying the granules;
mixing the dried granules with one or more pharmaceutical excipients to form a blend; and
compressing the blend into a tablet.

[15] The process according to claim 14 wherein the lactam content of the tablet does not exceed 0.6% by weight of gabapentin when the tablet is stored for three months at 40 ° C and 75% relative humidity

[16] The process according to claim 14 wherein the tablet provides therapeutically effective plasma levels of gabapentin for up to about 24 hours.

[17] The process according to claim 14 wherein gabapentin comprises between about 100 mg and about 1,200 mg by weight of the tablet.

[18] The process according to claim 14 wherein the hydroxypropylcellulose has a viscosity of between about 7 cps and about 30,000 cps.

[19] The process according to claim 17 wherein the hydroxypropylcellulose has a viscosity of between about 4,000 cps and about 15,000 cps.

[20] The process according to claim 14 wherein the polyvinylpyrrolidone derivative is selected from crospovidone, copolyvidone and physical mixtures of polyvinylpyrrolidone and polyvinylacetate.

[21] The process according to claim 14 wherein the polysaccharide gum is selected from the group consisting of guar gum, gum arabic, xanthan gum, locust bean gum, gum karaya and gum tragacanth or combinations thereof.

[22] The process according to claim 14 wherein the other pharmaceutical excipients are selected from diluents, binders, lubricants and glidant.

[23] The process according to claim 14 further comprising granulating one or more pharmaceutical excipients with the mixture of gabapentin and one or more hydrophilic rate-controlling polymers.

[24] A method of treating a medical condition, the method comprising providing an oral pharmaceutical sustained release tablet prepared from granules comprising gabapentin, one or more hydrophilic rate controlling polymers selected from the group consisting of hydroxypropylcellulose, polyvinylpyrrolidone and its derivatives, and polysaccharide gum and optionally one or more pharmaceutical excipients.

[25] The method of treatment according to claim 24 wherein the medical condition comprises one or both of epilepsy and neuropathic pain.

[26] The method of treatment according to claim 24 wherein the medical condition comprises epilepsy.

INTERNATIONAL SEARCH REPORT

IB2004/051408

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/195 A61K9/20 A61P25/08

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)
IPC 7 A61K A61P

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 practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 294 198 B1 (VILKOV ZALMAN) 25 September 2001 (2001-09-25) claims 3,5,9; tables 1-3	1-7, 9-20,22, 23
X	US 2003/008004 A1 (VILKOV ZALMAN) 9 January 2003 (2003-01-09) paragraph '0032!; claims 1,5,6,11,15,19	1-4,7, 9-17,20, 22,23
X	US 2002/091159 A1 (SPIREAS SPIRIDON) 11 July 2002 (2002-07-11) paragraphs '0004!, '0006!, '0010!, '0017!, '0038!, '0044!, '0045!, '0063!; claims 1,2,21,25,54,59,64; examples 13,20; tables 3,4,6	1-4,7, 9-17,20, 22,23

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"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)

"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

"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

"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

"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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 November 2004	10. 12. 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Uhl, M

INTERNATIONAL SEARCH REPORT

IB2004/051408

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03/103634 A (CHAWLA MANISH ; RAMPAL ASHOK (IN); RANBAXY LAB LTD (IN); RAGHUVANSHI R) 18 December 2003 (2003-12-18) page 3, line 22 - page 4, line 11 page 6, lines 13-21 page 9, line 28 - page 10, line 4 page 11, lines 13-18; claims 1-22; examples 4,5; table 1 -----	1-7, 9-20,22, 23

INTERNATIONAL SEARCH REPORT

PCT/IB2004/051408

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 24-26
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 24-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Continuation of Box II.1

Although claims 24-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.1

Claims Nos.: 24-26

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

IB2004/051408

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6294198 B1	25-09-2001	AU 6925400 A	19-03-2001
		WO 0113894 A1	01-03-2001
		US 2003008004 A1	09-01-2003
		US 2001043946 A1	22-11-2001
US 2003008004 A1	09-01-2003	US 2001043946 A1	22-11-2001
		US 6294198 B1	25-09-2001
		AU 6925400 A	19-03-2001
		WO 0113894 A1	01-03-2001
US 2002091159 A1	11-07-2002	AU 9473601 A	08-04-2002
		CA 2422871 A1	04-04-2002
		CN 1462186 T	17-12-2003
		EP 1322335 A2	02-07-2003
		NZ 524463 A	29-10-2004
		WO 0226263 A2	04-04-2002
WO 03103634 A	18-12-2003	WO 03103634 A1	18-12-2003