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(54) Title: SOLID PHARMACEUTICAL COMPOSITION OF GABAPENTIN

(57) Abstract: The present invention relates to solid pharmaceutical compositions of gabapentin that have good stability and good bioavailability of the active principle, and that can be used for preparing pharmaceutical solid forms of gabapentin for oral administration. The pharmaceutical composition of the invention is a solid composition comprising an intragranular phase and an extragranular phase. It is a solid composition that is of a granular appearance, but includes non-granulated particles of the extragranular phase. The invention lays on the incorporation of a hydrophobic compound in the intragranular phase, and a humectant in the extragranular phase which leads to the preparation of solid compositions of gabapentin that have good stability and good bioavailability of the gabapentin.



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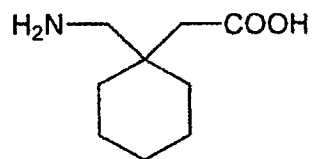
SOLID PHARMACEUTICAL COMPOSITION OF GABAPENTIN

5 Field of the invention

The present invention relates to solid pharmaceutical compositions of gabapentin that have good stability and good bioavailability of the active principle, and that can be used for preparing pharmaceutical forms of gabapentin for oral administration.

Prior art

Gabapentin is the INN of 1-aminomethyl-1-cyclohexaneacetic acid, corresponding to the following formula



and which was described for the first time in German patent application DE-A-2460891. The monohydrate of gabapentin is described in patent application EP-A-0340677, and the sodium and ammonium salts are described in US patent US4087544.

Gabapentin is used for treating cerebral diseases, for example as an antiepileptic, as well as for the treatment of neuropathic pain.

Gabapentin is known to have problems of stability, which arise in the manufacturing process of gabapentin and during storage, including in alkaline conditions. The causes of its instability have not been established exactly. Degradation of gabapentin leads to the formation of the internal lactam (4-cyclohexylpyrrolidone), and the simultaneous release of water, which causes problems additional to the

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stability of the solid dosage forms, such as, for example, tablets and capsules. Said lactam has a certain toxicity and its presence in the pharmaceutical composition must be avoided as far as possible. It is stipulated that its content in the final product must not exceed 0.5% (United States Pharmacopoeia, Pharmacopoeia Forum, Vol. 28(2), March - April 2002).

To minimize the conversion of gabapentin to lactam, in European patent application EP-A-0414263 it is proposed to keep the concentration of anions of mineral acid below 20 ppm and to use some defined excipients that do not promote the dehydration of gabapentin. The same patent application gives a list of excipients that reduce the stability of gabapentin: modified maize starch, croscarmellose sodium, glycerol behenate, methacrylic acid copolymers (types A and C), anion exchangers, titanium dioxide, and silicon gels such as Aerosil 200. The excipients were selected after laborious experimental work, since their catalytic activity cannot be predicted in a logical manner.

On the other hand, patent application WO-A-01/97612 states that the conditions mentioned in the previous patent application are not technically necessary for obtaining stable compositions of gabapentin. Said patent application describes stable compositions of gabapentin that contain a concentration of anions of mineral acid above 20 ppm, and excipients that should be avoided according to the description of EP-A-0414263. Criteria for selecting suitable excipients to form part of the gabapentin compositions are not proposed in said patent application either.

In view of the contradictory information that is encountered in the state of the art, it is difficult to identify excipients that are suitable for formulation in solid compositions of gabapentin.

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Various technical solutions for preparing stable compositions of gabapentin are described in the prior art.

5 Patent application EP-A-0446570 describes gabapentin tablets that contain maize starch, microcrystalline cellulose, and hydrogenated soya oil as lubricant. The same composition is also described in patent applications WO-A-01/97612 and WO-A-01/97782. None of
10 these includes data on the stability of the active principle in said tablet.

Controlled-release formulations of gabapentin that comprise a combination of an amphiphilic starch and
15 hydrogenated vegetable oil are described in patent application WO-A-2005/099674.

A capsule comprising gabapentin, microcrystalline cellulose, magnesium stearate, silica, and less than
20 0.05 wt.% of sodium lauryl sulphate as solubilizer is described in patent application WO-A-2005/072736.

Patent application WO-A-2006/008295 also describes capsules that comprise gabapentin and a mixture of
25 excipients formed from a calcium salt of a weak acid, for example tribasic calcium phosphate, and a lubricant selected from hydrogenated castor oil and glycerol behenate. Optionally they can also contain a diluent selected from the group comprising monosaccharide
30 sugars, and derivatives of polysaccharides.

Another way of minimizing the degradation of gabapentin is to use stabilizing compounds.

35 For example, patent application WO-A-02/26263 describes formulations that include a stabilizing compound that is able to reduce the ionic strength. Said compound is selected from the following classes of compounds: volatile alcohols, non-volatile alcohols, liquids or

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solids miscible with water, liquids or solids immiscible with water, liquid or solid surfactants, antioxidants, ketones and aldehydes.

- 5 Patent application WO-A-2005/051384 describes calcium carbonate as stabilizer for solid formulations of gabapentin.

10 In patent application WO-A-99/59573, a neutral amino acid is incorporated for stabilizing pharmaceutical compositions that contain gabapentin.

15 In patent application WO-A-99/59572, a humectant is included for stabilizing gabapentin formulations. Said humectant is selected from ethylene glycol, propylene glycol, butyl glycol, sorbitol, glycerol, or their esters with aliphatic acids.

20 However, the state of the art does not describe solid pharmaceutical compositions of gabapentin that contain a hydrophobic agent in an intragranular phase and a humectant in an extragranular phase, and owing to this disposition of the two excipients, the pharmaceutical forms prepared from said composition have good
25 stability and good bioavailability of the active principle. Therefore there is still a need for providing solid pharmaceutical compositions of gabapentin, as alternatives to those described in the state of the art.

30

Object of the invention

The object of the present invention is a solid pharmaceutical composition comprising gabapentin as active principle.

35

A tablet of gabapentin that comprises said composition also forms part of the object of the invention.

The use of the compositions for the preparation of solid forms of gabapentin for administration by the oral route also forms part of the invention.

5 Description of the invention

The present inventors have discovered that the incorporation of a hydrophobic compound in the intragranular phase, and a humectant in the extragranular phase, leads to the preparation of solid
10 compositions of gabapentin that have good stability and good bioavailability of the gabapentin.

The object of the invention is a solid pharmaceutical composition that comprises:

15

a) an intragranular phase comprising:

- i) a pharmaceutically effective amount of gabapentin,
- 20 ii) a hydrophobic compound selected from the group comprising hydrogenated vegetable oils, esters of glycerol and fatty acids with a C₁₆ to C₂₂ chain, alcohols with a C₁₆ to C₂₂ chain, cetyl esters, microcrystalline wax, and/or mixtures thereof, and
- 25 iii) an agglutinating agent, and

b) an extragranular phase that comprises a humectant selected from the group comprising anionic
30 surfactants, polyoxyethylenated esters of sorbitan and fatty acids with a C₁₂ to C₁₈ chain, polyoxyethylenated fatty acids with a C₁₆ to C₂₂ chain, and/or mixtures thereof.

35 The pharmaceutical composition of the invention is a solid composition comprising an intragranular phase and an extragranular phase. It is a solid composition that is of a granular appearance, but includes non-granulated particles of the extragranular phase.

The intragranular phase can be prepared by wet granulation of a mixture that comprises the active principle, a hydrophobic compound, and an agglutinating agent, according to conventional methods that are familiar to a person skilled in the art, such as those described in the book by Remington: The Science and Practice of Pharmacy, 20th Edition, Philadelphia, Lippincott, Williams & Wilkins, 2000 [ISBN 0 683 306472].

The extragranular phase comprises a humectant.

The composition of the invention is prepared by mixing the intragranular phase with the extragranular phase, and then homogenizing the mixture.

The active principle is gabapentin, and is selected from the group comprising its pharmaceutically acceptable salts, solvated, hydrated, or anhydrous. Among said compounds we may mention, for example, anhydrous gabapentin, gabapentin monohydrate, the sodium salt of gabapentin, and the calcium salt of gabapentin.

Gabapentin containing less than 20 ppm of chloride ions is preferably used in the compositions of the invention.

The physicochemical characteristics of said products, and of the other pharmaceutical excipients that are used for preparing the composition of the invention, are described in reference works that are accessible to a person skilled in the art, such as the Handbook of Pharmaceutical Excipients, 4th Edition, London, Pharmaceutical Press, 2003 [ISBN 0 85369 472 9]. These reference works also usually give the trade names under which said products are marketed.

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The hydrophobic compound that forms part of the intragranular phase is selected from the group comprising hydrogenated vegetable oils, esters of glycerol and fatty acids with a C₁₆ to C₂₂ chain, 5 alcohols with a C₁₆ to C₂₂ chain, cetyl esters, microcrystalline wax, and/or mixtures thereof.

Preferably the hydrophobic compound is a hydrogenated vegetable oil selected from the group comprising 10 hydrogenated castor oil, hydrogenated cottonseed oil, hydrogenated soya oil, hydrogenated palm oil, and/or mixtures thereof. More preferably the hydrophobic compound that forms part of the intragranular phase of the compositions of the invention is hydrogenated 15 castor oil.

The esters of glycerol and fatty acids with C₁₆ to C₂₂ chain that can be used in the compositions of the invention include glycerol palmitate, glycerol 20 stearate, glycerol palmitostearate, glycerol behenate, and/or mixtures thereof.

Alcohols with C₁₆ to C₂₂ chain that are suitable for use as hydrophobic compound in the compositions of the 25 invention include cetyl alcohol, cetostearyl alcohol, stearyl alcohol, behenic alcohol, and/or mixtures thereof.

Cetyl esters, which are defined as a mixture of esters 30 of saturated fatty alcohols with C₁₄ to C₁₈ chain and saturated fatty acids with C₁₄ to C₁₈ chain are also suitable for use in the compositions of the invention.

The microcrystalline wax comprises a mixture of 35 saturated linear and randomly branched alkanes obtained from petroleum. The length of the chains is in the range from C₄₁ to C₅₇.

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The agglutinating agent is a compound that is able to impart cohesive properties to the pulverulent materials constituting the intragranular phase, so that the characteristics of flowability of the composition are improved.

The agglutinating agent that is used for preparing the intragranular phase can be selected from the group comprising:

hydroxypropylcellulose,
hydroxypropylmethylcellulose, hydroxyethylcellulose,
methylcellulose, polyvinylpyrrolidone,
carboxymethylcellulose sodium, carboxymethylcellulose calcium, and/or mixtures thereof.

Preferably the agglutinating agent used is hydroxypropylcellulose.

The extragranular phase of the composition of the invention comprises a humectant.

A humectant is a compound or mixture of compounds that facilitates the wetting of the pharmaceutical composition when it comes into contact with water, so that it contributes to its dissolution, and to release of the active principle.

The humectant is selected from the group comprising anionic surfactants, polyoxyethylenated esters of sorbitan and fatty acids with C₁₂ to C₁₈ chain, polyoxyethylenated fatty acids with C₁₆ to C₂₂ chain, and/or mixtures thereof.

The anionic surfactants are compounds that possess one or more functional groups that become ionized in aqueous solution giving rise to organic ions with a negative charge, and are responsible for the surface activity, which include good wetting properties.

Preferably the humectant is an anionic surfactant.

Among the anionic surfactants, the following may be mentioned: soaps, alkyl sulphates, sulphonated paraffins, α -olefin sulphonates, dialkyl
5 sulphosuccinates, alkylbenzene sulphonates, alkyl phosphates and alkyl polyether sulphates.

Preferably the humectant used is sodium lauryl sulphate.

10

Sodium lauryl sulphate belongs to the alkyl sulphate group and is the sodium salt of the sulphuric monoester of lauric alcohol. It is an anionic surfactant with good humectant properties that finds application in
15 pharmaceutical, cosmetic, and detergent formulations.

Another anionic surfactant with good humectant properties is sodium docusate, which is included in the dialkyl sulphosuccinate group, and is the sodium salt
20 of bis(2-ethylhexyl) sulphosuccinate.

The polyoxyethylenated esters of sorbitan and fatty acids with C₁₂ to C₁₈ chain, also called polysorbates, are ionic surfactants that are prepared from sorbitan, obtained by dehydration of sorbitol, by esterification
25 with the corresponding fatty acid, and then reaction with ethylene oxide in the presence of a catalyst. The following may be mentioned: sorbitan monolaurate polyethoxylated with 20 mol of ethylene oxide, sorbitan monooleate polyethoxylated with 20 mol of ethylene
30 oxide, sorbitan monooleate polyethoxylated with 4 mol of ethylene oxide, sorbitol trioleate polyethoxylated with 20 mol of ethylene oxide.

35 The polyoxyethylenated fatty acids with C₁₆ to C₂₂ chain are non-ionic surfactants obtained from the reaction of a fatty acid with C₁₆ to C₂₂ chain with ethylene oxide in the presence of a catalyst. Consideration may also be given to esters of fatty acids with C₁₆ to C₂₂ chain

and a polyethylene glycol of molecular weight between 40 and 8000. Within this group we may mention, for example: stearate of polyethylene glycol 400, stearate of polyethylene glycol 6000. The number that
5 accompanies the name of the product corresponds to the average molecular weight of the polyethylene glycol chain that is incorporated in the ester.

In the compositions of the invention the amount of
10 gabapentin can vary between 75% and 95% based on the total weight of the composition, preferably between 80% and 90% based on the total weight of the composition; the amount of hydrophobic compound can vary between 3% and 15% based on the total weight of the composition,
15 preferably between 6% and 12% based on the total weight of the composition; the amount of humectant can vary between 1% and 5% based on the total weight of the composition, preferably between 2% and 4% based on the total weight of the composition, and the amount of
20 agglutinating agent can vary between 1% and 5% based on the total weight of the composition, preferably between 2% and 4% based on the total weight of the composition.

The compositions of the invention can be used for the
25 preparation of solid pharmaceutical forms of gabapentin for administration by the oral route.

Preferred among the oral pharmaceutical forms are tablets, which can be obtained by mixing and
30 homogenizing the compositions of the invention with suitable excipients, followed by compression.

The invention also relates to a tablet of gabapentin that comprises an amount of the composition of the
35 invention that is sufficient to provide an effective unit dose of gabapentin, and at least one excipient.

Preferably the tablets of the invention comprise between 70 wt.% and 90 wt.% of the composition of the

invention, and between 10 wt.% and 30 wt.% of at least one excipient. More preferably the tablets comprise between 75 wt.% and 85 wt.% of the composition of the invention, and between 15 wt.% and 25 wt.% of at least one excipient.

As already mentioned, gabapentin is a very effective active principle for the treatment of cerebral diseases such as epilepsy and neuropathic pain, and has extremely low toxicity. However, to maintain the therapeutic effect it is usually administered to adults at daily doses between 900 mg and 2400 mg, divided into three doses. Preferably the tablets of the invention contain a unit dose that is between 300 mg and 800 mg of gabapentin.

It has been verified that in the tablets containing the formulations of the invention, selection of the excipient is not critical.

The excipient can be selected from the group comprising diluents, disintegrants, lubricants, antiadherents, sweeteners, flavour enhancers, flavouring agents, and/or mixtures thereof.

The excipient can be incorporated either in the granulation stage for preparing the intragranular phase, or in the stage of mixing of the latter with the extragranular phase together with the humectant, or alternatively in both stages.

The diluents are inert excipients that facilitate compression of pulverulent materials and endow the tablets with strength. They can be incorporated both in the intragranular phase and in the extragranular phase. The following are included among the diluents that can be used: microcrystalline cellulose, cellulose powder, silicated cellulose, lactose monohydrate, anhydrous

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lactose, mannitol, sorbitol, sucrose, fructose, dextrose, and/or mixtures thereof.

Preferably the diluent used in the tablets of the invention is microcrystalline cellulose.

The disintegrants are excipients that cause the tablet to break up rapidly when placed in an aqueous medium, plus rapid disaggregation of the granules, so that the active principle is released quickly. Preferably said excipients are incorporated in the extragranular phase. The disintegrants can be selected from the group comprising: hydroxypropylcellulose of low degree of substitution, carboxymethylcellulose sodium, carboxymethylcellulose calcium, crospovidone, croscarmellose sodium, and/or mixtures thereof.

Preferably the disintegrant used is hydroxypropylcellulose of low degree of substitution.

The lubricants and antiadherents are excipients that reduce interparticle tension, prevent adhesion of the particles, and improve the flowability of granulated or pulverulent compositions. The lubricants can be selected from the group comprising talc, alkaline earth salts of stearic acid, especially magnesium and calcium stearates, stearic acid, glycerol palmitostearate, stearyl fumarate, and/or mixtures thereof. One of the antiadherents used most commonly is colloidal silica.

Preferably magnesium stearate is used as lubricant.

The tablets of this invention can in addition contain sweeteners, flavouring agents and flavour enhancers, with the aim of obtaining adequate organoleptic characteristics (aroma and taste) that will be acceptable to the patient. Among the sweeteners, we may mention saccharin sodium, aspartame, mannitol, xylitol, sucrose, sorbitol and ammonium glycyrricinate, and

among the flavouring agents and flavour enhancers we may mention flavours from fruits and plants, for example orange, anise, mint, etc.

5 The amount of excipient present in the tablets of the invention will vary depending on the type of excipient used. For example the amount of diluent can be between 1% and 10% based on the total weight of the tablet, preferably between 3% and 7% based on the total weight
10 of the tablet; the amount of disintegrant can be between 5% and 15% based on the total weight of the tablet, preferably between 7% and 12% based on the total weight of the tablet; and the amount of lubricant can be between 0.5% and 3% based on the total weight of
15 the tablet, preferably between 1% and 2% based on the total weight of the tablet.

For the purposes of the invention, the tablet preferably comprises gabapentin, hydrogenated castor
20 oil as hydrophobic compound, sodium lauryl sulphate as humectant, hydroxypropylcellulose as agglutinating agent, microcrystalline cellulose as diluent, hydroxypropylcellulose of low degree of substitution as disintegrant, and magnesium stearate as lubricant.

25 In a preferred embodiment the tablets of the invention comprise between 65 wt.% and 75 wt.% of gabapentin, between 5 wt.% and 7 wt.% of hydrogenated castor oil, between 1 wt.% and 3 wt.% of sodium lauryl sulphate,
30 between 2 wt.% and 4 wt.% of hydroxypropylcellulose, between 3 wt.% and 7 wt.% of microcrystalline cellulose, between 7 wt.% and 12 wt.% of hydroxypropylcellulose of low substitution, and between 1 wt.% and 2 wt.% of magnesium stearate.

35 In a more preferred embodiment the tablets of the invention comprise between 68 wt.% and 72 wt.% of gabapentin, between 5.5 wt.% and 6.5 wt.% of hydrogenated castor oil, between 1.5 wt.% and 2.5 wt.%

of sodium lauryl sulphate, between 2.5 wt.% and 3.5 wt.% of hydroxypropylcellulose, between 4 wt.% and 6.5 wt.% of microcrystalline cellulose, between 8 wt.% and 11.2 wt.% of hydroxypropylcellulose of low substitution, and between 1.2 wt.% and 1.8 wt.% of magnesium stearate.

In all the embodiments of the invention the sum of the percentages by weight of the components of the tablets is equal to 100%.

In a preferred embodiment the tablets of the invention comprise:

- a) between 300 and 800 mg of gabapentin
- b) between 28 and 75 mg of hydrogenated castor oil
- c) between 6 and 16 mg of sodium lauryl sulphate
- d) between 10 and 28 mg of hydroxypropylcellulose
- e) between 19 and 52 mg of microcrystalline cellulose
- f) between 40 and 107 mg of hydroxypropylcellulose of low substitution, and
- g) between 6 and 16 mg of magnesium stearate.

The tablets of the invention can be prepared by methods that are familiar to a person skilled in the art, and are fully described in Remington's book cited above.

One possible way of preparing the tablet is for example as follows. Mix and sieve the active principle and the hydrophobic compound, and granulate said mixture by wet granulation by applying a solution of an agglutinating agent and a solvent, which can be water or an organic solvent. Dry the granulated mixture in a fluidized bed, and sieve. Then add the humectant to the dry granules previously prepared and carry out compression in a conventional machine. The excipient can be incorporated in the granulation stage, and/or before compression of the granular composition.

Once the tablet has been obtained, if desired it is possible to apply an outer layer of protective coating, again using conventional techniques, for example by
5 sugar coating or spraying.

In a preferred embodiment, the tablet includes in addition an outer coating layer.

10 In this case it is possible to use known coatings that are available in the marketplace such as LUSTRE CLEAR, which is formed from a mixture of carragenate and microcrystalline cellulose, and in addition pigments and opacifiers such as titanium dioxide.

15 With the compositions of the invention, it is also possible to prepare capsules that comprise an amount of the composition that is sufficient to provide an effective unit dose of gabapentin.

20 In the case of a capsule the unit dose of gabapentin is between 100 mg and 400 mg, since larger amounts of active principle require the use of excessively large capsules.

25 The capsules of the invention can be prepared by methods that are familiar to a person skilled in the art, and are well described in Remington's book previously cited; for example using a capsule filling
30 machine in which the composition of the invention is distributed into hard gelatin capsules.

Surprisingly it was found that the compositions of the invention have good stability both in normal storage
35 conditions (36 months at a temperature of $25 \pm 2^\circ\text{C}$ and relative humidity of $60 \pm 5\%$), and in accelerated stability conditions (12 months at a temperature of $30 \pm 2^\circ\text{C}$ and relative humidity of $60 \pm 5\%$). Thus, the tablets prepared using the compositions of the

invention have good stability in both storage conditions, and in all cases the lactam content remained below 0.4 wt.% determined by high-performance liquid chromatography (HPLC). This result shows that, despite the intense interaction to which the active principle and the excipients are submitted during the compression process, the compositions of the invention do not promote the reaction of dehydration of gabapentin that leads to the formation of lactam.

It has also been verified that the presence of the hydrophobic compound in the intragranular phase, and of the humectant in the extragranular phase of the compositions of the invention makes it possible to prepare tablets of gabapentin that release the active principle gradually over a period of time of approximately one hour, which gives good bioavailability of the active principle.

The following example will now be presented for the purpose of completing the above description in a sufficient manner:

Example 1. Preparation of tablets containing 800 mg of gabapentin

800 g of gabapentin, 40 g of microcrystalline cellulose 50 μ m, and 74.66 g of hydrogenated castor oil were weighed. They were then sieved in a vibratory sieve, and mixed.

A solution of 28.00 g of hydroxypropylcellulose in 140 g of purified water was prepared.

The aforementioned mixture was mixed with the aqueous solution of hydroxypropylcellulose in a fast, high-shear granulator.

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The mixture was dried in a fluidized bed at a temperature not above 40°C, and the dry granules were sieved at a mesh of 1 mm, thus obtaining the intragranular phase of the composition of the invention.

Next, 12.00 g of microcrystalline cellulose 100 µm, and 106.66 g of hydroxypropylcellulose LH21 were weighed, sieved in a vibratory sieve, and mixed with the intragranular phase obtained previously.

16.00 g of sodium lauryl sulphate and 16.00 g of magnesium stearate were weighed, sieved, and added to the previous mixture, and then homogenized.

The mixture obtained was compressed in a rotary tablet press, obtaining 1000 tablets of gabapentin with a content of active principle of 800 mg.

Finally, the tablets were coated with an aqueous dispersion formed from 6.00 g of titanium dioxide, 26.00 g of LUSTRE CLEAR, and 320 g of water, so that the increase in tablet weight on applying the coating was about 3%.

The tablets obtained displayed good stability both in normal storage conditions (36 months at a temperature of $25 \pm 2^\circ\text{C}$ and relative humidity of $60 \pm 5\%$), and in accelerated stability conditions (12 months at a temperature of $30 \pm 2^\circ\text{C}$ and relative humidity of $60 \pm 5\%$).

The stability results for different parameters in the two sets of environmental conditions are presented in Table I:

TABLE I

Parameter	Specifications	36 months at $25 \pm 2^\circ\text{C}$ and $60 \pm 5\%$	12 months at $30 \pm 2^\circ\text{C}$ and $60 \pm 5\%$
Appearance	White coated tablet	Correct	Correct
Water content (%, KF)	< 3	1.78	1.53
Assay (%, HPLC)	95.0-105.0	97.6	100.8
Lactam (%, HPLC)	≤ 0.4	0.38	0.36
Hardness (N)	110-180	138.3	149.1
Disintegration in water	< 30'	21'28"	20'49"
Microbiological quality	$\leq 10^3$ total aerobic bacteria $\leq 10^2$ fungi per g or ml Absence of <i>E.</i> <i>coli</i>	Correct	Correct

The values of the parameters shown in Table I were determined according to the methods stated below.

- 5 The water content was determined using the Karl Fischer method, which is familiar to a person skilled in the art.
- 10 The assay value, or content of active principle, and the content of lactam impurity were determined using HPLC following the method described in section 2.2.29 of the European Pharmacopoeia.
- 15 Tablet hardness was determined in the manner described in section 2.9.8 of the European Pharmacopoeia.

Tablet disintegration in water was determined following the guidelines given in section 2.9.1 of the European Pharmacopoeia.

- 5 Microbiological quality was determined by the usual methods of microbiological control, such as those described in section 5.1.4 (Category 3) of the European Pharmacopoeia.
- 10 The dissolution profile exhibited by the tablets of the invention is suitable for releasing 100% of the active principle in a space of time of approximately 1 hour.

- The dissolution test was performed according to the
- 15 method described in section 2.9.3 of the European Pharmacopoeia.

The experimental conditions of said test are:

<u>Parameter</u>	<u>Value</u>
Substrate	6 tablets of 800 mg of gabapentin
Medium	Hydrochloric acid 0.06 N
Volume	900 ml
Temperature of the medium	37°C ± 0.5°C
Stirring	50 rpm

20

To establish the complete release profile, samples were taken at different times (5, 10, 15, 20, 30, 45 and 60 minutes), they were filtered through a 0.45 µm filter, and the gabapentin content was determined by HPLC.

25

The mean values of the percentage of gabapentin dissolved as a function of time for the tablets prepared according to the method described in Example 1 are shown in Table II:

- 20 -

TABLE II

Time (minutes)	%
0	0.0
5	20.0
10	28.0
15	51.0
20	62.0
30	92.0
45	99.0
60	100.0

It can be seen that the active principle is released gradually in 30 minutes, and release is completed
5 between 45 and 60 minutes. This release profile is suitable for providing correct bioavailability of gabapentin.

Patent claims

1. Solid pharmaceutical composition, characterized
5 in that it comprises:
- a) an intragranular phase comprising:
 - i) a pharmaceutically effective amount of gabapentin
 - ii) a hydrophobic compound selected from the group comprising hydrogenated vegetable oils, esters of glycerol and fatty acids with a C₁₆ to C₂₂ chain, alcohols with a C₁₆ to C₂₂ chain, cetyl esters, microcrystalline wax, and/or mixtures thereof, and
 - iii) an agglutinating agent, and
 - b) an extragranular phase that comprises a humectant selected from the group comprising anionic
10 surfactants, polyoxyethylenated esters of sorbitan and fatty acids with a C₁₂ to C₁₈ chain, polyoxyethylenated fatty acids with a C₁₆ to C₂₂ chain, and/or mixtures thereof.
- 15 2. Composition according to Claim 1, characterized in that the gabapentin is selected from the group comprising its pharmaceutically acceptable salts, solvated, hydrated, and anhydrous.
- 20 3. Composition according to Claim 2, characterized in that the gabapentin contains less than 20 ppm of chloride ions.
4. Composition according to any one of Claims 1 to
25 3, characterized in that the hydrophobic compound is a hydrogenated vegetable oil selected from the group comprising hydrogenated castor oil, hydrogenated cottonseed oil, hydrogenated soya oil, hydrogenated palm oil, and/or mixtures thereof.

5. Composition according to Claim 4, characterized in that the hydrophobic compound is hydrogenated castor oil.
- 5 6. Composition according to any one of Claims 1 to 5, characterized in that the agglutinating agent is selected from the group comprising: hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, methylcellulose, 10 polyvinylpyrrolidone, carboxymethylcellulose sodium, carboxymethylcellulose calcium, and/or mixtures thereof.
7. Composition according to Claim 6, characterized 15 in that the agglutinating agent is hydroxypropylcellulose.
8. Composition according to any one of Claims 1 to 7, characterized in that the humectant is an anionic 20 surfactant.
9. Composition according to Claim 8, characterized in that the humectant is sodium lauryl sulphate.
- 25 10. Composition according to any one of Claims 1 to 9, characterized in that the amount of gabapentin is between 75% and 95% based on the total weight of the composition.
- 30 11. Composition according to any one of Claims 1 to 10, characterized in that the amount of hydrophobic compound is between 3% and 15% based on the total weight of the composition.
- 35 12. Composition according to any one of Claims 1 to 11, characterized in that the amount of humectant is between 1% and 5% based on the total weight of the composition.

13. Composition according to any one of Claims 1 to 12, characterized in that the amount of agglutinating agent is between 1% and 5% based on the total weight of the composition.

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14. Tablet of gabapentin, characterized in that it comprises an amount of the composition according to any one of Claims 1 to 13 that is sufficient to provide an effective unit dose of gabapentin, and at least one

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15. Tablet according to Claim 14, characterized in that it comprises between 70 wt.% and 90 wt.% of the composition according to any one of Claims 1 to 13, and

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16. Tablet according to Claim 15, characterized in that it comprises between 75 wt.% and 85 wt.% of the composition according to any one of Claims 1 to 13, and

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17. Tablet according to any one of Claims 14 to 16, characterized in that it comprises between 300 and 800 mg of gabapentin.

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18. Tablet according to any one of Claims 14 to 17, characterized in that the excipient is selected from the group comprising diluents, disintegrants, lubricants, antiadherents, sweeteners, flavour enhancers, flavouring agents, and/or mixtures thereof.

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19. Tablet according to any one of Claims 14 to 18, characterized in that it comprises microcrystalline cellulose as diluent.

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20. Tablet according to any one of Claims 14 to 19, characterized in that it comprises hydroxypropylcellulose of low degree of substitution as disintegrant.

21. Tablet according to any one of Claims 14 to 20, characterized in that it comprises magnesium stearate as lubricant.

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22. Tablet according to any one of Claims 14 to 21, characterized in that it comprises gabapentin, hydrogenated castor oil, microcrystalline cellulose, hydroxypropylcellulose, sodium lauryl sulphate,
10 hydroxypropylcellulose of low degree of substitution, and magnesium stearate.

23. Tablet according to Claim 22, characterized in that it comprises between 65 wt.% and 75 wt.% of
15 gabapentin, between 5 wt.% and 7 wt.% of hydrogenated castor oil, between 1 wt.% and 3 wt.% of sodium lauryl sulphate, between 2 wt.% and 4 wt.% of hydroxypropylcellulose, between 3 wt.% and 7 wt.% of microcrystalline cellulose, between 7 wt.% and 12 wt.%
20 of hydroxypropylcellulose of low substitution, and between 1 wt.% and 2 wt.% of magnesium stearate.

24. Tablet according to Claim 23, characterized in that it comprises between 68 wt.% and 72 wt.% of
25 gabapentin, between 5.5 wt.% and 6.5 wt.% of hydrogenated castor oil, between 1.5 wt.% and 2.5 wt.% of sodium lauryl sulphate, between 2.5 wt.% and 3.5 wt.% of hydroxypropylcellulose, between 4 wt.% and 6.5 wt.% of microcrystalline cellulose, between 8 wt.%
30 and 11.2 wt.% of hydroxypropylcellulose of low substitution, and between 1.2 wt.% and 1.8 wt.% of magnesium stearate.

25. Tablet of gabapentin according to any one of
35 Claims 14 to 24, characterized in that it comprises:

- a) between 300 and 800 mg of gabapentin
- b) between 28 and 75 mg of hydrogenated castor oil
- c) between 6 and 16 mg of sodium lauryl sulphate

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- d) between 10 and 28 mg of hydroxypropylcellulose
- e) between 19 and 52 mg of microcrystalline cellulose
- f) between 40 and 107 mg of hydroxypropylcellulose
- 5 of low substitution, and
- g) between 6 and 16 mg of magnesium stearate.

26. Tablet according to any one of Claims 14 to 25,
characterized in that in addition it includes an outer
10 coating layer.

27. Use of the compositions according to Claims 1
to 13 for preparing solid pharmaceutical forms of
gabapentin for administration by the oral route.
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