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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING LAMOTRIGINE

(57) Abstract

A pharmaceutical formulation comprises: (a) from 0.5 to 50 % by weight of lamotrigine or a pharmaceutically acceptable acid addition salt thereof, (b) from 15 to 50 % by weight of lactose, (c) from 15 to 50 % by weight of starch, (d) from 0.5 to 15 % by weight of crystalline cellulose, and (e) from 5 to 15 % by weight of polyvinylpyrrolidone, and which is in the form of a free-flowing powder of granules having the following properties: (i) no granules have a particle size of greater than 850 μm, (ii) at least 90 % by weight of the granules have a particle size of from 75 to 850 μm, (iii) the granules disintegrate within 30 minutes according to the Disintegration Test of The Pharmacopoeia of Japan, twelfth edition, 1991, and (iv) at least 90 % by weight of the lamotrigine or lamotrigine salt in the granules dissolves within 30 minutes when the granules are subjected to the Dissolution Test, method 2 (paddle method) of The Pharmacopoeia of Japan, twelfth edition, 1991.

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PHARMACEUTICAL COMPOSITION COMPRISING LAMOTRIGINE

The present invention relates to a pharmaceutical formulation of lamotrigine and pharmaceutically acceptable acid addition salts thereof. The invention also relates to the preparation of such a formulation.

Lamotrigine is 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine. It is disclosed in EP-A-0021121. Lamotrigine is useful for the treatment of epilepsy. No powder formulation of lamotrigine or one of its salts is currently available.

Pharmaceutical formulations in powder form can be prepared by a fluid bed granulating process or spray granulation. However, such processes represent a complex interaction of processing variables.

We have now prepared a number of powder formulations of lamotrigine. Only one type of formulation, however, proved to be entirely satisfactory. Accordingly, the present invention provides a pharmaceutical formulation which comprises:

(a) from 0.5 to 50% by weight of lamotrigine or a pharmaceutically acceptable acid addition salt thereof,

(b) from 15 to 50% by weight of lactose,

(c) from 15 to 50% by weight of starch,

(d) from 0.5 to 15% by weight of crystalline cellulose, and

(e) from 5 to 15% by weight of polyvinylpyrrolidone,

and which is in the form of a free-flowing powder of granules having the following properties:

(i) no granules have a particle size of greater than 850μm,

(ii) at least 90% by weight of the granules have a particle size of from 75 to 850μm,

(iii) the granules disintegrate within 30 minutes according to the Disintegration Test of The Pharmacopoeia of Japan, twelfth edition, 1991, and

(iv) at least 90% by weight of the lamotrigine or

lamotrigine salt in the granules dissolves within 30 minutes when the granules are subjected to the Dissolution Test, method 2 (paddle method) of The Pharmacopoeia of Japan, twelfth edition, 1991.

The formulation of the invention is provided by a process which comprises spray-granulating:

(a) from 0.5 to 50% by weight of lamotrigine or a lamotrigine salt,

(b) from 15 to 50% by weight of lactose,

(c) from 15 to 50% by weight of starch, and

(d) from 0.5 to 15% by weight of crystalline cellulose,

in the presence of, as a binder:

(e) from 5 to 15% by weight of polyvinylpyrrolidone.

The granules of which the powder of the invention is composed are agglomerates. The lamotrigine or lamotrigine salt is provided on particles of lactose and starch which each act as an adsorbent bulking agent. A homogenous powder mixture comprising components (a) to (d) may be formed as a pre-blend prior to starting the spray granulation procedure. The presence of the lactose aids the formation of this pre-blend. The crystalline cellulose confers disintegrant and dissolution properties on the granules. The polyvinylpyrrolidone acts as a binder.

Any suitable lamotrigine salt which is a pharmaceutically acceptable acid addition salt can be used. Preferred salts are the methanesulphonate and isethionate salts. These salts can be made by reacting lamotrigine as the free base with the appropriate acid.

Preferably up to 98% by weight of the granules of the invention have a particle size of from 75 to 850μm. At least 92% by weight of the granules may have such a particle size, for example from 92 to 95% by weight of the granules. Preferably no more than 5% by weight of the granules have a particle size greater than 500μm, for example no more than 3% by weight. Desirably, no granules

at all have a particle size greater than 500μm. Particle size is determined by the Particle Size Distribution Test for Powders, The Pharmacopoeia of Japan, twelfth edition, 1991.

Typically, at least 90% by weight of the lamotrigine or lamotrigine salt in the granules is dissolved within 15 minutes according to the Dissolution Test, method 2 (paddle method). The amount of lamotrigine dissolved is determined by an appropriate physicochemical technique, for example by ultraviolet (UV) analysis or by high pressure liquid chromatography (hplc).

The powder of the invention is generally dust-free. It is preferably white although it may be white to off-white. A colourant could be present, though. It is free-flowing, as may be determined by the eye. Typically the bulk density of the powder is from 0.3 to 0.6 g/cm^3, for example from 0.35 to 0.50 g/cm^3 or from 0.36 to 0.40 g/cm^3. Residual moisture levels are generally from 0.5 to 5.0% by weight, for example from 1 to 3% by weight.

Preferred formulations contain from 0.5 to 30% by weight of lamotrigine or a lamotrigine salt. Formulations may thus contain from 0.5 to 20% by weight, for example from 0.5 to 15% by weight or from 1 to 10% by weight, of lamotrigine or a lamotrigine salt. Particularly preferred are formulations containing 1%, 2%, 5% or 10% by weight of lamotrigine or a lamotrigine salt.

The amounts of lactose and starch in the formulations are greater the smaller the amount of lamotrigine or lamotrigine salt that is present. The starch is preferably corn starch. Suitable amounts of lactose and starch may be from 15 to 45% by weight, for example from 30 to 45% by weight or from 35 to 45% by weight or from 40 to 45% by weight. Preferably the amount of lactose is 70 to 130%, for example 90 to 110%, the amount of starch. Typically, the amounts of lactose and starch are the same.

The powders of the invention may contain from 3 to 8% by weight, for example from 3.5 to 6% by weight, of

crystalline cellulose. Powders containing 5% by weight of crystalline cellulose are preferred.

Preferably the amount of polyvinylpyrrolidone present is from 5 to 10% by weight, for example from 6 to 9% by weight, of the formulation. Powders containing 8% by weight of polyvinvylpyrrolidone are preferred.

A preferred formulation of the invention comprises:

(a') from 0.5 to 15% by weight of lamotrigine or a lamotrigine salt,

(b') from 35 to 45% by weight of lactose,

(c') from 35 to 45% by weight of starch,

(d') from 3.5 to 6% by weight of crystalline cellulose, and

(e') from 6 to 9% by weight of polyvinylpyrrolidone.

An especially preferred formulation comprises 1% by weight of lamotrigine, 43% by weight of each of lactose and starch, 5% by weight of crystalline cellulose and 8% by weight of polyvinylpyrrolidone. Another especially preferred formulation comprises 10% by weight of lamotrigine, 38.5% by weight of each of lactose and starch, 5% by weight of crystalline cellulose and 8% by weight of polyvinylpyrrolidone.

A formulation of the invention is prepared by a process which comprises spray-granulating the lamotrigine or lamotrigine salt, lactose, starch, crystalline cellulose in the presence of, as a binder, the polyvinylpyrrolidone. The lamotrigine salt, lactose, starch and crystalline cellulose are each provided as powders having particle sizes, for example average particle sizes, well below 850μm and, indeed, below 200μm. These four components may be pre-blended as a uniform mixture prior to the spray granulation step.

A solution of polyvinylpyrrolidone is prepared as a binder solution. The solution may be an aqueous or aqueous/ethanolic solution. A proportion of the polyvinylpyrrolidone, for example from 30 to 60% by weight or more especially 50% by weight, may be pre-blended with

the lamotrigine or lamotrigine salt, lactose, starch and crystalline cellulose.

A fluid bed granulation process is employed to obtain the powder of the invention. A rotary-type fluid granulator is typically used. The lamotrigine or lamotrigine salt, lactose, starch and crystalline cellulose are introduced in powder form into the granulator, for example as a pre-blended mixture. The binder solution is sprayed onto the fluidising powder. The particles of the fluidising powder adhere to one another. The desired granules form. The conditions under which granulation is effected can be adjusted as appropriate.

The granules thus obtained may be sieved to ensure that the appropriate particle size requirements are met. Thus, the granules may be sieved through a sieve of 850μm mesh size to ensure no granules having a particle size of greater than 850μm are present. Further, the granules may be sieved through a sieve of 500μm mesh size to ensure that no more than 5% by weight of the granules have a particle size greater than 500μm. Yet further, the granules may be sieved through a sieve of 75μm mesh size. Indeed, the granules obtained from the granulator may be passed to a sieve stack fitted with 850, 500 and 75μm sieves. Oversized and undersized materials are rejected.

The lamotrigine or lamotrigine salt employed as a starting material typically has a particle size of 125μm or less. The starting lactose generally has a particle size of below 250μm, especially 200μm or less such as from 50 to 200μm. The lactose may be an anhydrous lactose, for example direct compression lactose such as Lactose DCL21, or lactose monohydrate.

The particle sizes of Lactose DCL21 and another grade of lactose that can be used, Lactose DMV200, are as follows:

DCL 21		DCL 200 II	
	Approx		Approx
> 50μm	85%	> 45μm	40-50%
> 150μm	40%	> 63μm	17-22%
> 250 μm	5%	> 100 μm	1-7%
> 355 μm	0%	> 160 μm	0-1%
		> 250 μm	0%

The starch may be rice, wheat or corn starch. Corn starch is alternatively termed maize starch and is preferred. A powder of starch of a particle size of from 30 to 150μm is typically used as a starting material. The starch may be a partially pregelatinised starch such as Starch 1500 manufactured by Colorcon, Indianapolis, Indiana 46218, US, or a fully gelatinised starch such as National 1551.

The crystalline cellulose typically is a powder of, for example, an average particle size of from 40 to 100μm such as from 50 to 90μm. A suitable crystalline cellulose is Avicel PH 102 having an average particle size of 90μm. Crystalline cellulose is alternatively called microcrystalline cellulose.

Any suitable polyvinylpyrrolidone capable of acting as a binder can be employed. The polyvinylpyrrolidone may be a linear polymer of 1-vinyl-2-pyrrolidone having an average molecular weight of about 40000, such as Povidone K30. Alternatively, a linear polymer of 1-vinyl-2-pyrrolidone having an average molecular weight of about 1200000, such as Povidone K90, may be employed.

The powder that is produced by spray granulation and, if necessary, subsequent sieving is then introduced into a container which is then closed. The container may be sealed. It may be a single-dose or multi-dose container. The container may be jar, bag or sachet. Sachets, especially foil sachets, are particularly suitable.

The following Examples illustrate the invention.

Example 1

1 Kg of each of five powders was prepared by spray granulation. The formula for each powder is as follows:

Formula A (comparison)

Lamotrigine 125μm	1.0% by weight
Lactose Fastflo	91.0% by weight
Povidone K30 British Pharmacopoeia (BP)	8.0% by weight

Lamotrigine 125μm is lamotrigine having particle sizes up to 125μm. Lactose Fastflo is an anhydrous spray-dried lactose manufactured by Wisconsin Dairies, Baraboo, Wisconsin 53913, U.S..

Formula B (comparison)

Lamotrigine 125μm	1.0% by weight
Lactose Fastflo	43.0% by weight
Lactose DCL21	43.0% by weight
Povidone K30 BP	8.0% by weight
Hydroxypropylcellulose low substitution (LHPC-11)	5.0% by weight

Formula C (invention)

Lamotrigine 125μm	1.0% by weight
Lactose DCL21	43.0% by weight
Pregelatinised Maize (Corn) Starch BP/USNF (Starch 1500)	43.0% by weight
Microcrystalline cellulose BP (Avicel PH 102)	5.0% by weight
Povidone K30 BP	8.0% by weight

Formula D (comparison)

Lamotrigine 125μm	1.0% by weight
Pregelatinised Maize (Corn) Starch BP/USNF (Starch 1500)	86.0% by weight
Hydroxypropylcellulose	

low substitution (LHPC-11) . . . . . 5.0% by weight
Povidone K30 BP . . . . . 8.0% by weight

Formula E (comparison)
Lamotrigine 125μm . . . . . 1.0% by weight
Pregelatinised Maize Starch
BP/USNF (Starch 1500) . . . . . .91.0% by weight
Povidone K30 BP . . . . . 8.0% by weight

Formula C was spray-granulated as follows as 2 x 5 kg sub-lots:

1. A Povidone binder solution was prepared and stored at room temperature.

2. The pregelatinised starch was passed through a 250μm sieve to remove any large agglomerates.

3. The lamotrigine, lactose, starch and Avicel PH102 were pre-blended in a Collette mixer as a precautionary measure to facilitate uniform lamotrigine distribution.

4. The powder was spray-granulated in a Glatt GPCG5 granulator using a Schlick spray gun of nozzle aperture 1.2mm utilising atomising air at a pressure of 2 bars. The binder solution pumping rate was approximately 90ml per minute. The inlet air temperature was controlled at 72°C and an air volume of between 150-250m^3 per hour was utilised to provide sufficient fluidisation to allow drying and granulation to occur simultaneously. The drier bags were shaken for approximately 6 seconds at 1.5 minute intervals to remove fine powder.

5. During granulation the product temperature was recorded. This temperature was typically 32-34°C but once spraying had been completed this rose shortly afterwards to 45-50°C indicating that final drying was occurring. The overall process time was of the order of 1 hour per sub-lot.

6. The two sub-lots of granules were then blended in a large polythene bag and finally sieved through a

Russell Finex sieve using screen of 710μm and 100μm to remove under and over-sized components of the granules.

Formulae A, B, D and E were spray-granulated in analogous fashion. Powders of free-flowing white granules were obtained in the case of formulae A to C and E. Formula D gave a powder which was severely overmassed. A substantial proportion of particles were oversize. This powder was not therefore satisfactory and was not tested further. The properties of the powders obtained from formulae A to C and E are as follows:

Formula	A	B	C	E
Yield %	91.8	80.5	87.4	86.3
Moisture %	0.68	1.21	2.46	0.65
Untamped Bulk Density g/cm^3	0.40	0.53	0.37	0.50
% by weight of granules over 850μm in size	0%	0%	0%	0%
% by weight of granules over 500μm in size	4.8	1.2	8.1	2.0
% by weight of granules over 75μm in size	94.8	97.8	92.5	97.4
Disintegration Test *	Complies	Complies	Complies	Complies

* Disintegration Test, The Pharmacopoeia of Japan, twelfth edition, 1991.

Initially, 9.8% by weight of the powder obtained from formula B did not pass through a 500μm sieve. The powder was therefore resieved through a 500μm sieve. Subsequent sieve analysis showed that only 1.2% of the powder then did not pass through a 500μm test sieve. Different 500μm sieves were used for the resieving and the subsequent testing, which accounts for why some powder still did not

pass through the 500μm test sieve.

Example 2

General

The effect of temperature, humidity and artificial light was studied on the stability of the powders obtained in Example 1 according to formulae A to C and E. The powders were stored for two months at 40°C and 75% relative humidity (R.H.) in both amber glass bottles closed with plastic caps and open amber glass bottles. They were also stored at 50°C and 60°C for 2 months in amber glass bottles closed with plastic caps. Further, they were stored at 25°C under artificial light conditions (1000 lux) for up to 1.2 million lux.hr total irradiation.

Test Items

The following parameters were monitored to evaluate the stability of the formulations:

1. Appearance

2. Loss on drying

Conditions of 60°C in vacuo for 3 hours were employed for formulae A and B. Conditions of 60°C in vacuo for 6 hours were employed for formulae C and E. These test conditions were decided with reference to the test conditions of lactose and starch in The Pharmacopoeia of Japan, twelfth edition, 1991.

3. Assay and related substances

A lamotrigine assay and a purity test were conducted by high pressure liquid chromatography (hplc).

4. Dissolution test

Dissolution of the powders was studied using the Dissolution Test, method 2 (paddle method) of The

Pharmacopoeia of Japan, twelfth edition, 1991. The time points of sampling were 15, 30 and 45 min and 0.1 N hydrochloric acid was used as the test solution. Lamotrigine was detected by ultraviolet absorption.

Results

1. Appearance

Under 40°C and 75% R.H., all of the powders in open glass bottles formed lumps in the high humidity and had turned pale yellowish white in colour. The colour of, in particular, the powder of formula B easily changed under severe conditions compared to the colour of the other particles. Results are shown in Tables 1 to 5 below.

2. Loss on drying

Formula E was the most hygroscopic powder. The results are shown in Tables 1 to 5.

3. Assay and related substances

From the degradation point of view, the most stable powder was that obtained from formula E and the most unstable powder was that from formula A under the high humidity conditions such as 40°C, 75% R.H., open glass bottle conditions.

4. Dissolution test

All of the formulations showed rapid dissolution. More than 90% of the lamotrigine in each powder was dissolved within 15 minutes.

Table 1: Granules Stored under 40°C, 75% R.H. Conditions (Container: Closed Glass Bottles).

Test Items	Formula	Storage Period		
		Initial	1 month	2 months
Appearance	A	White powder	White powder	White powder
	B	White powder	White powder	Pale yellowish white powder
	C	White powder	White powder	White powder
	E	White powder	White powder	White powder
Loss on Drying (n=3, % by weight)	A	1.15 ± 0.10*	1.40 ± 0.01	1.23 ± 0.02
	B	1.63 ± 0.16	1.67 ± 0.02	1.81 ± 0.07
	C	4.29 ± 0.12	4.98 ± 0.17	4.78 ± 0.01
	E	7.27 ± 0.16	7.44 ± 0.07	7.24 ± 0.02

* : Mean ± S.D.

Table 2: Granules Stored under 40°C, 75% R.H. Conditions (Container: Open Glass Bottles).

Test Items	Formula	Storage Period		
		Initial	1 month	2 months
Appearance	A	White powder	Pale yellowish white cake	Pale yellowish white cake
	B	White powder	Pale yellowish white cake	Pale yellowish white cake
	C	White powder	Pale yellowish white cake	Pale yellowish white cake
	E	White powder	Pale yellowish white cake	Pale yellowish white cake
Loss on Drying (n=3, % by weight)	A	1.15 ± 0.10*	1.03 ± 0.31	2.15 ± 0.02
	B	1.63 ± 0.16	1.05 ± 0.03	2.65 ± 0.03
	C	4.29 ± 0.12	3.69 ± 0.20	8.24 ± 0.09
	E	7.27 ± 0.16	6.66 ± 0.24	14.32 ± 0.03

* : Mean ± S.D.

Table 3: Granules Stored under 50°C Condition (Container: Closed Glass Bottles).

Test Items	Formula	Storage Period		
		Initial	1 month	2 months
Appearance	A	White powder	White powder	White powder
	B	White powder	White powder	White powder
	C	White powder	White powder	White powder
	E	White powder	White powder	White powder
Loss on Drying (n=3, % by weight)	A	1.15 ± 0.10*	0.94 ± 0.11	0.59 ± 0.15
	B	1.63 ± 0.16	1.57 ± 0.19	1.05 ± 0.13
	C	4.29 ± 0.12	4.12 ± 0.11	3.76 ± 0.15
	E	7.27 ± 0.16	7.04 ± 0.12	6.57 ± 0.14

* : Mean ± S.D.

Table 4: Granules Stored under 60°C Condition (Container: Closed Glass Bottles).

Test Items	Formula	Storage Period		
		Initial	1 month	2 months
Appearance	A	White powder	White powder	White powder
	B	White powder	Pale yellowish white powder	Pale yellowish white powder
	C	White powder	Pale yellowish white powder	Pale yellowish white powder
	E	White powder	White powder	White powder
Loss on Drying (n=3, % by weight)	A	1.15 ± 0.10*	0.58 ± 0.11	0.42 ± 0.03
	B	1.63 ± 0.16	0.75 ± 0.14	0.64 ± 0.08
	C	4.29 ± 0.12	3.61 ± 0.11	3.13 ± 0.04
	E	7.27 ± 0.16	6.71 ± 0.17	6.03 ± 0.03

* : Mean ± S.D.

Table 5: Granules Stored under 25°C, 1000 lux Irradiation (Container: Glass Dishes).

Test Items	Formula	Storage Period		
		Initial	0.6 million lux.hr	1.2 million lux.hr
Appearance	A	White powder	White powder	White powder
	B	White powder	White powder	White powder
	C	White powder	White powder	White powder
	E	White powder	White powder	White powder
Loss on Drying (n=3, % by weight)	A	1.15 ± 0.10*	-**	1.43 ± 0.06
	B	1.63 ± 0.16	-	1.90 ± 0.03
	C	4.29 ± 0.12	-	5.34 ± 0.05
	E	7.27 ± 0.16	-	9.03 ± 0.07

* : Mean ± S.D.
** : Not examined

Conclusion

Formula A (comparison)

The powder of this formulation was stable under high temperature conditions without humidity. Under high humidity conditions, however, it became slightly unstable.

Formula B (comparison)

The powder of this formulation was stable under high temperature conditions without humidity. However, it changed colour the most easily. Under high humidity conditions it became slightly unstable.

Formula C (invention)

The powder of this formulation was stable under high temperature conditions without humidity. It was also stable under high humidity conditions.

Formula E (comparison)

The powder of this formulation was stable under high temperature conditions without humidity. It was also stable under high humidity conditions. Under high humidity conditions, however, it absorbed the most moisture.

Example 3

Powders were prepared by spray granulation of each of the following formulae:

	Formula 1	Formula 2
Lamotrigine 125μm	1.0% by weight	10.0% by weight
Lactose, DMV 200 mesh	43.0% by weight	38.50% by weight
Starch 1500	43.0% by weight	38.50% by weight
Avicel PH102	5.0% by weight	5.0% by weight
Povidone K30	8.0% by weight	8.0% by weight

50g of lamotrigine 125μm and 2150g of each of Lactose DMV 200 mesh and Starch 1500 (Formula 1) or 500g of lamotrigine 125μm and 1925g of each of Lactose DMV 200 mesh and Starch 1500 (Formula 2) were mixed together with 250g of Avicel PH102 and 200g of Povidone K30 in a Collette Planetary mixer for 3 minutes. An approximately uniform pre-blend of powders is thus produced.

Separately, 200g of Povidone K30, the second half of the Povidone K30, was dissolved in 600ml of demineralised water. That was then made up to 1000ml to give a 20% solids solution. This was used as the granulating solution.

The pre-blend of powders was added to a Freund SFC rotor granulator. This is a type of fluid bed granulator and provides a rotary type fluidization action on powders in order to achieve a suitable granule distribution. The

granulating solution was sprayed onto the fluidizing powders as a fine mist via an air type spray gun system. The addition of the granulating solution in this way resulted in the powders adhering together to form suitably sized granule particles. The process was continued until all the granulating solution had been added and the granules were of a suitable size.

More especially the following parameters were used on the Freund SFC granulator:

1) Inlet air temperature 80°C
2) Rotor speed 300 rpm
3) Agitator speed 450rpm
4) Chopper speed 1500rpm
5) Inlet air Volume 2.9m^3/hr
6) Atomizing air pressure 4kg/cm^2
7) Spray Nozzle Size 1.8mm
8) Spray rate 45g/min

Using these parameters the required granules were produced employing:

1) Inlet air temperature 75-80°C
2) Outlet air temperature 28-32°C
3) Product temperature 28-35°C
4) Air Volume 2.9-3.0m^3/hr
5) Spray rate 40-43g/min
6) Time to granulate powders 22min
7) Time to dry granule 11 min

The prepared granules were then passed through a sieve fitted with 850, 500 and 75μm sieves. The granules were sieved to the desired particle size requirements. In particular, no granules had a particle size greater than 850μm. At least 90% by weight of the granules had a particle size of from 75 to 850μm. Not more than 5% by weight of the granules had a particle size of greater than 500μm. The oversized and undersized granules were used.

Each powder has the following further properties:

(i) the granules disintegrate within 30 minutes according to the Disintegration Test of The Pharmacopoeia

of Japan, twelfth edition, 1991, and

(ii) at least 90% by weight of the lamotrigine dissolves within 30 minutes according to the Dissolution Test, method 2 (paddle method) of The Pharmacopoeia of Japan, twelfth edition, 1991.

CLAIMS

1. A pharmaceutical formulation which comprises:

(a) from 0.5 to 50% by weight of lamotrigine or a pharmaceutically acceptable acid addition salt thereof,

(b) from 15 to 50% by weight of lactose,

(c) from 15 to 50% by weight of starch,

(d) from 0.5 to 15% by weight of crystalline cellulose, and

(e) from 5 to 15% by weight of polyvinylpyrrolidone,

and which is in the form of a free-flowing powder of granules having the following properties:

(i) no granules have a particle size of greater than 850μm,

(ii) at least 90% by weight of the granules have a particle size of from 75 to 850μm,

(iii) the granules disintegrate within 30 minutes according to the Disintegration Test of The Pharmacopoeia of Japan, twelfth edition, 1991, and

(iv) at least 90% by weight of the lamotrigine or lamotrigine salt in the granules dissolves within 30 minutes when the granules are subjected to the Dissolution Test, method 2 (paddle method) of The Pharmacopoeia of Japan, twelfth edition, 1991,

2. A formulation according to claim 1, which comprises:

(a') from 0.5 to 15% by weight of lamotrigine or a lamotrigine salt,

(b') from 35 to 45% by weight of lactose,

(c') from 35 to 45% by weight of corn starch,

(d') from 3.5 to 6% by weight of crystalline cellulose, and

(e') from 6 to 9% by weight of polyvinylpyrrolidone.

3. A formulation according to claim 2, which comprises 1% by weight of lamotrigine, 43% by weight of each of lactose and starch, 5% by weight of crystalline cellulose and 8% by weight of polyvinylpyrrolidone.

4. A formulation according to claim 2, which comprises 10% by weight of lamotrigine 38.5% by weight of each of lactose and starch, 5% by weight of crystalline cellulose and 8% by weight of polyvinylpyrrolidone.

5. A formulation according to any one of the preceding claims, wherein not more than 5% by weight of the granules have a particle size of greater than 500μm.

6. A formulation according to any one of the preceding claims, wherein the powder has a bulk density of from 0.36 to 0.40 g/cm^3.

7. A formulation according to any one of the preceding claims, wherein the starch is corn starch.

8. A process for the preparation of a pharmaceutical formulation which comprises

(a) from 0.5 to 50% by weight of lamotrigine or a pharmaceutically acceptable acid addition salt thereof,

(b) from 15 to 50% by weight of lactose,

(c) from 15 to 50% by weight of starch,

(d) from 0.5 to 15% by weight of crystalline cellulose, and

(e) from 5 to 15% by weight of polyvinylpyrrolidone,

and which is in the form of a free-flowing powder of granules having the following properties.

(i) no granules have a particle size of greater than 850μm,

(ii) at least 90% by weight of the granules have a particle size of from 75 to 850μm,

(iii) the granules disintegrate within 30 minutes according to the Disintegration Test of The Pharmacopoeia of Japan, twelfth edition, 1991, and

(iv) at least 90% by weight of the lamotrigine or lamotrigine salt in the granules dissolves within 30 minutes when the granules are subjected to the Dissolution Test, method 2 (paddle method) of The Pharmacopoeia of Japan, twelfth edition, 1991,

which process comprises spray-granulating the lamotrigine

or lamotrigine salt, lactose, corn starch and crystalline cellulose in the presence of, as a binder, polyvinylpyrrolidone.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 95/02865

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/53 A61K9/00 A61K9/20

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 6 A61K

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FR,A,2 702 149 (RHONE-POULENC RORER S.A.) 9 September 1994 see page 2, line 23 - line 27 see examples A,B	1-8
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Y	WO,A,94 21260 (THE WELLCOME FOUNDATION LIMITED) 29 September 1994 see example 4	1-8
Y	WO,A,94 21261 (THE WELLCOME FOUNDATION LIMITED) 29 September 1994 see example 2	1-8

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[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

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 March 1996	12. 03. 96

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	Scarponi, U

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