STABLE SUSTAINED-RELEASE ORAL DOSAGE FORMS OF GABAPENTIN AND PROCESS FOR PREPARATION THEREOF

Field of the Invention

Provided herein are stable sustained-release oral dosage forms of gabapentin, processes for preparation thereof, and uses thereof in treating epilepsy or post herpetic neuralgia.

Background of the Invention

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 are inherent in the drug, which 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. However, 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 the same should be within safe permissible limits.

Gabapentin (1-(aminomethyl)cyclohexaneacetic acid) is a γ-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 is also being used to treat neuropathic pain.

Gabapentin has been reported to convert to a toxic lactam compound (Impurity A) during preparation and storage. This lactam formation is also seen in formulations containing gabapentin. The cause of lactam formation in formulation during storage is apparently also the catalytic effects of 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 8000mg/kg, while that of the corresponding lactam is 300mg/kg.

Consequently, these impurities and the potential formation of such decomposition products during storage of pharmaceutical compositions must be reduced to minimum for reasons of safety.

U.S. Patent No. 6,054,482 discloses pharmaceutical excipients that are incompatible with gabapentin and do not have any noticeable influence on the stability of gabapentin. The list of excipients includes, *inter alia*, hydroxypropylmethylcellulose. However, when gabapentin is formulated with hydroxypropyl methylcellulose, an increase in lactam content is observed, rendering the formulation to be highly unstable upon storage.

The incompatibility of gabapentin with some commonly-used and readily available pharmaceutical excipients, particularly rate-controlling polymers, restricts the number of compatible excipients and makes it difficult to develop a stable sustained-release dosage form having desired release characteristics of gabapentin. A process which makes compatible a larger number of available excipients for use in the preparation of stable sustained-release dosage forms of gabapentin is needed. In view of the instability of gabapentin in typical dosage forms and its short half life, there is a need for a sustained-release dosage form of gabapentin that is stable during storage, has low lactam content and provides therapeutically effective plasma levels of gabapentin over prolonged period. Such stable sustained-release dosage forms of gabapentin would not only provide a safe mode of gabapentin therapy, but also 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.

Summary of the Invention

Provided herein are stable sustained-release tablets of gabapentin comprising an intragranular component, which comprises gabapentin and optionally one or more rate controlling polymers; and an extragranular component, which comprises one or more rate-controlling polymers, wherein lactam content does not exceed 0.4 % by weight of gabapentin when the tablet is kept for about 3 months at about 40 °C and about 75 % relative humidity. The one or more intragranular rate-controlling polymers and one or more extragranular rate controlling polymers can be the same or different.

Embodiments of the stable sustained-release tablets may include one or more of the following features. For example, the intragranular component can comprise one or more rate controlling polymers. The one or more rate-controlling polymers in the intragranular component (*i.e.*, the one or more intragranular rate-controlling polymers) and the extragranular component the one or more rate-controlling polymers in the extragranular component (*i.e.*, the one or more extragranular rate-controlling polymers) together can comprise from about 5 % to about 80 % by weight of the tablet. The one or more rate-controlling polymers in the intragranular component can comprise from about 0 % to about 50 % by weight of the granules and the one or more rate-controlling polymers in the extragranular component can comprise from about 5 % to about 80 % by weight of the tablet.

The intragranular or extragranular rate-controlling polymers can also be one or more of polyvinylpyrrolidone or derivatives thereof; a cellulosic polymer; a vinyl acetate copolymer; an alginate; xanthan gum; guar gum; starch; a starch-based polymer; polyethylene oxide; a methacrylic acid copolymer; a maleic anhydride/methyl vinyl ether copolymer or derivatives thereof; ethyl cellulose; cellulose acetate; a methacrylate; an acrylic acid polymer or copolymer; a high molecular weight polyvinyl alcohol; a wax; or mixtures thereof.

The cellulosic polymer can be one or more of hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, methylcellulose or mixtures thereof. In some embodiments, the sustained-release tablets contain hydroxypropylmethylcellulose having a viscosity of about 100 cps to about 100,000 cps, a viscosity of about 15,000 cps or even a viscosity of about 4000 cps. In other embodiments, the sustained-release tablets contain hydroxypropylcellulose having a viscosity of about 7 cps to about 30,000 cps, a viscosity of about 1000 cps to about 15000 cps, or even a viscosity of about 4000 cps.

The sustained-release tablets can further comprise one or more additional pharmaceutical excipients, for example, diluents, lubricants, glidants, binders or mixtures thereof. The diluents can be one or more of powdered sugar, calcium phosphate, calcium sulphate, microcrystalline cellulose, lactose, mannitol, kaolin, dry starch, sorbitol or mixtures thereof. The lubricants can be one or more of talc, stearic acid, vegetable oil, calcium stearate, zinc stearate, magnesium stearate or mixtures thereof. The glidants can

be one or more of talc, silicon dioxide, corn starch or mixtures thereof. The binders can be one or more of polyvinylpyrrolidone, polyvinylpyrrolidone/vinylacetate copolymer, xanthan gum, guar gum, cellulose gums (*e.g.*, carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose), gelatin, starch pregelatinized starch or mixtures thereof.

In another general aspect there is provided processes for preparing a stable sustained-release tablet of gabapentin comprising the steps of granulating a mixture comprising gabapentin, one or more pharmaceutical excipients and optionally one or more rate-controlling polymers with a granulating liquid to form an intragranular component; drying, sizing and mixing the intragranular component with one or more extragranular rate-controlling polymers to form a blend, and compressing the blend into a tablet. Such stable sustained-release tablets have a lactam content that does not exceed 0.4 % by weight of gabapentin when the tablet is kept for about 3 months at about 40 °C and about 75 % relative humidity. The optional one or more intragranular rate-controlling polymers and the one or more extragranular rate-controlling polymers can be the same or different.

Embodiments of the processes may include one or more of the following features. For example, the intragranular component of the tablets disclosed herein can be prepared by wet granulation or dry granulation. Dry granulation can be carried out by compacting or slugging.

In another general aspect there is provided processes for preparing a stable sustained-release tablet of gabapentin comprising the steps of mixing gabapentin, one or more pharmaceutical excipients and optionally one or more rate-controlling polymers to form a mixture; compacting or slugging the mixture to form compacts or slugs; sizing the compacts or slugs to form granules; mixing the granules with one or more extragranular rate-controlling polymers to form a blend; and compressing the blend into tablets. Such stable sustained-release tablets have a lactam content that does not exceed 0.4 % by weight of gabapentin when the tablet is kept for about 3 months at about 40 °C and about 75 % relative humidity. The optional one or more intragranular rate-controlling polymers and the one or more extragranular rate-controlling polymers can be the same or different.

In yet another general aspect there is provided methods for treating epilepsy or post herpetic neuralgia comprising administering to a patient in need thereof a stable sustained-

release tablet of gabapentin comprising: an intragranular component comprising a therapeutically effective amount of gabapentin and optionally one or more rate-controlling polymers; and an extragranular component comprising one or more rate-controlling polymers, wherein lactam content does not exceed 0.4 % by weight of gabapentin when the tablet when kept for about 3 months at about 40 °C and about 75 % relative humidity and wherein the optional one or more intragranular rate-controlling polymers. The one or more extragranular rate-controlling polymers can be the same or different.

In another aspect there is provided tablets prepared by processes comprising the steps of granulating a mixture comprising gabapentin, one or more pharmaceutical excipients and optionally one or more intragranular rate-controlling polymers with a granulating liquid to form an intragranular component; drying, sizing and mixing the intragranular component with one or more extragranular rate-controlling polymers to form a blend, and compressing the blend into a tablet.

In yet another aspect there is provided tablets prepared by processes comprising the steps of mixing gabapentin, one or more pharmaceutical excipients and optionally one or more intragranular rate-controlling polymers to form a mixture; compacting or slugging the mixture to form compacts or slugs; sizing the compacts or slugs to form granules; mixing the granules with one or more extragranular rate-controlling polymers to form a blend; and compressing the blend into tablets.

Detailed Description of the Invention

It has been surprisingly observed that for a given rate-controlling polymer, the stability of gabapentin tablet is influenced by the amount of the rate-controlling polymer that is present intragranularly or extragranularly. In particular, the stability is improved when the amount of rate-controlling polymer is decreased in the intragranular component.

The processes described herein provide flexibility and broaden the number of suitable pharmaceutical excipients, particularly rate-controlling polymers, for preparing stable sustained-release dosage forms of gabapentin. Rate-controlling polymers, which would typically show incompatibility with gabapentin, can be used to prepare stable compositions using the processes disclosed herein when a portion of the rate-controlling

polymers is utilized extragranularly in the dosage form. The processes are economical and can be easily carried out to prepare stable sustained-release tablets of gabapentin that provide therapeutically effective plasma levels of gabapentin for a period of up to about 24 hours. Granules can be prepared by wet granulation or dry granulation process.

Excipients, particularly rate-controlling polymers which are typically incompatible with gabapentin, can be used in gabapentin compositions without compromising the stability of gabapentin. This can be achieved by either extragranular addition of one or more rate-controlling polymers, or intragranular addition of one portion of one or more rate-controlling polymers and extragranular addition of the remaining portion of the one or more rate-controlling polymers. Such processes result in improved stability of gabapentin compositions when compared to formulations having all of their rate-controlling polymers in an intragranular component. In addition, the processes and tablets provided herein result in gabapentin compositions having reduced lactam content.

Thus in one embodiment granules can be prepared by blending gabapentin, other pharmaceutical excipients and optionally one or more rate-controlling polymers to form a blend and granulating the blend with a granulating liquid to form a intragranular component; drying the intragranular component; sizing the intragranular component; mixing the intragranular component with one or more rate-controlling polymers and one or more additional extragranular excipients; and compressing to make tablets.

In another embodiment granules can be prepared by blending gabapentin, other pharmaceutical excipients and optionally a part of rate-controlling polymer to form a blend; compacting or slugging the blend; sizing; mixing with one or more rate-controlling polymers and other additional extragranular excipients; and compressing to make tablets.

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

Gabapentin may be present as a free base, hydrated form (*e.g.*, a monohydrate) or any other pharmaceutically acceptable salt thereof. Gabapentin may comprise from about 100 mg to about 1200 mg by weight of the tablet.

The rate-controlling polymer may be either hydrophilic or hydrophobic in nature; particularly suitable are rate-controlling polymers that swell in aqueous media. The

amount of rate-controlling polymers in the tablet relative to gabapentin depends upon the rate of drug release required, as well as the type and molecular weight of the rate-controlling polymers and other excipients present in the formulation. The rate-controlling polymer may be present intragranularly and extragranularly (*i.e.*, in the intragranular component or the extragranular component) or may present only in the extragranular component. The intragranular or extragranular rate-controlling polymers may be the same type or different types. The amount of intragranular rate-controlling polymer may depend on its type and also on the extent of its incompatibility with gabapentin. In general, the total amount of the rate-controlling polymer in the dosage form (*i.e.*, the amount of intragranular rate-controlling polymer together with the amount of extragranular rate-controlling polymer) may vary from about 5 % to about 80 % by weight of the tablet, from about 10 % to about 70%, and even from about 15 %to 60% by weight of the tablet. The intragranular rate-controlling polymer may comprise from about 0% to about 50% by weight of the granules or by weight of the tablet while the extragranular rate-controlling polymer may comprise from 5% to about 80% by weight of the tablet.

Examples of suitable rate-controlling polymers (extragranular or intragranular) include polyvinylpyrrolidone (PVP) and derivatives thereof (*e.g.*, copolyvidone, mixtures of PVP and polyvinylacetate, for example, Kollidon SR); cellulosic polymers (*e.g.*, hydroxypropyl methylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, methylcellulose); vinyl acetate copolymers; polysaccharides (such as alginate, xanthan gum, guar gum etc.); starch, starch-based polymers or mixtures thereof; polyethylene oxide; methacrylic acid copolymers; maleic anhydride/methyl vinyl ether copolymers; or derivatives or mixtures thereof. Particularly suitable rate-controlling polymers include hydroxypropyl methylcellulose, hydroxypropylcellulose or a mixture thereof.

Hydroxypropyl methylcellulose can have different viscosities, for example, having a viscosity from about 100 cps to about 100,000 cps, and even from about 4000 cps to about 15,000 cps. Suitable types of hydroxypropyl methylcellulose are sold under the trade name METHOCEL by Dow Chemical Co., for example, METHOCEL K4MCR, METHOCEL K15MCR and METHOCEL K100MCR. Hydroxypropylcellulose can also have different viscosities, including those sold by, for example, Aqualon under the brand name of KLUCEL, and also by Nippon Soda Co. Ltd, Japan. Suitable

hydroxypropylcellulose include those having viscosities of from about 7 to about 30,000 cps, from about 1000 to about 15,000 cps, and even from about 4000 to about 15,000 cps. In addition to the above, rate-controlling polymers also include cellulose derivatives (*e.g.*, ethyl cellulose or cellulose acetate), methacrylates, acrylic acid polymers or copolymers, high molecular weight polyvinyl alcohols or waxes (*e.g.*, fatty acids or glycerides).

The sustained-release gabapentin tablets as described herein may further comprise one or more additional additives or pharmaceutical excipients such as diluents, lubricants, binders, glidants etc.

Suitable diluents include, for example, one or more of powdered sugar, calcium phosphate, calcium sulfate, microcrystalline cellulose, lactose, mannitol, kaolin, dry starch, sorbitol, and the like, or mixtures thereof.

Suitable lubricants include one or more of talc, stearic acid, vegetable oil, calcium stearate, zinc stearate, magnesium stearate or mixtures thereof.

Suitable glidants include one of more of talc, silicon dioxide, cornstarch, or mixtures thereof.

Suitable binders include one or more of polyvinylpyrrolidone, polyvinylpyrrolidone/vinyl acetate copolymer; xanthan gum, guar gum; cellulose ethers (*e.g.*, carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose or mixtures thereof); gelatin, starch or derivatives thereof; or mixtures thereof.

Suitable granulating liquids include, for example, one or more of water, ethanol, isopropyl alcohol, acetone, dichloromethane, and the like, or mixtures thereof.

Suitable binders can be dissolved in suitable granulating liquids and used as a solution/dispersion.

Processes for the preparation of stable gabapentin sustained-release tablets include the steps of:

1. granulating a mixture comprising gabapentin and optionally one or more rate-controlling polymers with a solution/dispersion of one or more binders to form granules (*i.e.*, an intragranular component);

2. drying granules (*i.e.*, intragranular component) and mixing the granules (*i.e.*, intragranular component) with one or more rate-controlling polymers and one or more additional pharmaceutical excipients (*e.g.*, one or more diluents, lubricants, glidants, binders, or mixtures thereof) to form a blend, and compressing the blend into a tablet by suitable methods.

Processes for the preparation of stable gabapentin sustained-release tablets include the steps of:

1. granulating a mixture comprising gabapentin and hydroxypropylcellulose with a solution/dispersion of hydroxypropylcellulose to form granules (*i.e.*, an intragranular component);

2. drying and mixing the granules with hydroxypropylmethylcellulose or hydroxypropylcellulose and one or more additional pharmaceutical excipients (*e.g.*, diluents, lubricants, glidants, binders, or mixtures thereof) to form a blend, and compressing the blend into a tablet by suitable methods.

Tablets can also be coated with one or more non-rate-controlling polymers, for example, OPADRY® sold by Colorcon, to impart aesthetic appeal. Such coatings can comprise about 2% by weight of the tablet.

Stable sustained-release tablets of gabapentin as described herein may be used, for example, in the treatment of patients suffering from epilepsy of post herpetic neuralgia.

Also encompassed herein are methods for treating epilepsy or post herpetic neuralgia in a patient comprising administering to the patient in need thereof one or more stable sustained-release tablet of gabapentin as disclosed herein.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.

The stable gabapentin tablets described herein is further illustrated by the following examples but these should not be construed as limiting the scope of the invention.

Examples

The following examples describe procedures in formulating the compositions of Examples 1-8 listed in Table 1.

Examples 1 and 2

Gabapentin was mixed with a portion of hydroxypropylcellulose and granulated with a second portion of hydroxypropylcellulose dissolved in purified water. The granules were dried, sized, mixed with extragranular hydroxypropylmethylcellulose, mannitol, copolyvidone, poloxamer, magnesium stearate and talc and compressed to form a tablet (Example 1); or hydroxypropylmethylcellulose, hydroxypropylcellulose, mannitol, copolyvidone, poloxamer, magnesium stearate and talc and compressed to form a tablet (Example 2).

Examples 3 and 4

Gabapentin was mixed with a portion of hydroxypropylcellulose and granulated with second portion of hydroxypropylcellulose dissolved in isopropyl alcohol/dichloromethane mixture. The granules were dried and sized, mixed with the extragranular portion of hydroxypropylcellulose, mannitol, copolyvidone, poloxamer, magnesium stearate and talc and compressed to form a tablet.

Example 5

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, poloxamer, magnesium stearate and talc and compressed to form a tablet.

Example 6

Gabapentin was mixed with a portion of hydroxypropylmethylcellulose and granulated with remaining portion of hydroxypropylmethylcellulose dissolved in purified water. The granules were dried and sized, mixed with mannitol, copolyvidone, poloxamer, magnesium stearate and talc and compressed to form a tablet.

Example 7

Gabapentin was mixed with a portion of hydroxypropylmethylcellulose and granulated with remaining portion of hydroxypropylmethylcellulose dissolved in purified water. The granules were dried and sized, mixed with extragranular hydroxypropylmethylcellulose, mannitol, copolyvidone, poloxamer, magnesium stearate and talc and compressed to form a tablet.

Example 8

Gabapentin was mixed with a portion of hydroxypropylcellulose and granulated with the remaining portion of hydroxypropylcellulose dissolved in isopropyl alcohol. The granules were dried, mixed with hydroxypropylmethylcellulose, mannitol, copolyvidone, poloxamer, magnesium stearate and talc and compressed to form a tablet.

Example 9

Gabapentin was mixed with a portion of hydroxypropylcellulose and granulated with second portion of hydroxypropylcellulose dissolved in isopropyl alcohol. The granules were dried and sized, mixed with hydroxypropylmethylcellulose, mannitol, copolyvidone, poloxamer, magnesium stearate and talc and compressed to form a tablet.

Example 10

Gabapentin was mixed with a portion of hydroxypropylcellulose and granulated with second portion of hydroxypropylcellulose dissolved in isopropyl alcohol. The granules were dried and sized, mixed with hydroxypropylmethylcellulose and the extragranular portion of hydroxypropylcellulose, mannitol, copolyvidone, poloxamer, magnesium stearate and talc and compressed to form a tablet.

Table 1 Compositions of Formulations of Examples 1-8

Ingredient	Quantity (mg) Ex. 1	Ex. 2	Ex. 3	Ex. 4	Ex. 5	Ex. 6	Ex. 7	Ex. 8	Ex. 9	Ex. 10
Intragranular										
Gabapentin	900	900	900	900	900	900	900	900	600	450
Hydroxypropylcellulose	39	39	128	55	265	--	--	55	36.7	27.5
Hydroxypropylmethylcellulose	--	--	--	--	--	100	50	--	--	--
Extragranular										
Hydroxypropylmethylcellulose	100	100	--	--	--	--	50	225	150	112.5
Hydroxypropylcellulose	--	50	150	225	--	--	--	--	--	50
Mannitol	161.5	111.5	10.5	10.5	15.5	81	81	10.5	13.7	10.26
Copolyvidone	12	12	12	12	12	12	12	12	8	6
Poloxamer	15	15	15	15	15	12	12	15	10	7.5
Magnesium stearate	20	20	20	20	20	15	15	20	13.3	10
Talc	22.5	22.5	22.5	22.5	22.5	15	15	22.5	15	11.25
Total	**1270**	**1270**	**1258**	**1260**	**1250**	**1135**	**1135**	**1260**	**846.7**	**685**

Table 2 Compositions of Formulations of Examples A-G

Ingredient	Quantity (mg)						
	A	**B**	**C**	**D**	**E**	**F**	**G**
Intragranular							
Gabapentin	900	900	900	900	900	900	900
Hydroxypropylcellulose	--	39	100	100	120	20	120
Hydroxypropylmethylcellulose	100	100	--	--	--	--	--
Mannitol	81	37	--	--	--	--	--
Extragranular							
Hydroxypropylmethylcellulose	--	--	--	--	--	100	--
Mannitol	--	--	83.73	95.73	60.5	60.5	60.5
Copolyvidone	12	8	12	--	12	12	12
Poloxamer	12	10	12	12	15	15	15
Magnesium stearate	15	10	15	15	20	20	20
Talc	15	10	15	15	22.5	22.5	22.5
Total	**1135**	**775**	**1137.7**	**1137.7**	**1150**	**1150**	**1150**

Stability testing

The fundamental aims of accelerated stability testing are to ensure that the product will be safe and efficacious when administered to the patient after being subjected to the anticipated stresses of storage, transport and administration. The product should remain free from toxic substances and the content of active ingredients should comply with the label claim until the expiry date. The real time stability testing of a dosage form under normal conditions of storage may stretch for years. The storage of a dosage form under accelerated conditions of temperature and relative humidity provides an approximate idea about the stability of the dosage form in the actual usage. For stability testing over a short period of time, we have developed a correlation between the lactam produced in a formulation when stored for 14 days at 60 °C and 75 % relative humidity (RH) and the same produced at 40 °C and 75 % RH when stored for 3 months in sealed HDPE bottles. The compositions of Examples A-G have been tested under these conditions of storage and are listed in Table 2. The lactam content ranges from about 0. to about 1.5 for formulations stored for 14 days at 60 °C and 75 % RH and from about 0.23 to about 1.4 for formulations stored for 3 months at 40 °C and 75 % RH. The correlation between the lactam content of these formulations under these two conditions of storage was used to develop a correlation between the two stability conditions and is described by the equation of a straight line ($R^2 = 0.9706$):

$$y = 0.6797x + 0.0515$$

where, y = lactam content produced at 40°C/75 % RH at 3 month, and x = lactam content produced at 60°C/75 % RH at 14 days. By this correlation, it is implied that a 0.5% w/w of lactam in a formulation stored for 14 days at 60 °C and 75 % RH corresponds to 0.4 %w/w of lactam in that formulation stored for 3 months at 40 °C and 75 % RH.

When the formulations of Examples 1-8 were stored for 3 months at 40 °C and 75 % relative humidity, the lactam content in these formulations was found to be in accordance with the developed correlation *i.e.*, the lactam content determined in these formulations when stored for 14 days at 60°C and 75% RH could effectively predict the lactam content in the same formulations when stored for 3 months at 40 °C and 75 % RH using the developed correlation described above. The stability data showed that stability of gabapentin

formulation is substantially increased as the portion of intragranular rate-controlling polymer is decreased.

The tablets of Examples 1, 2 and 8, which contain extragranular hydroxypropyl methylcellulose, were more stable in comparison to the tablets of Examples 6 and 7, which contain intragranular hydroxypropyl methylcellulose. Tablets of Examples 1, 2 and 8 exhibited an initial lactam content of about 0.025 % (w/w), a lactam content of between about 0.25 % to about 0.36 % (w/w) after storage for 14 days at 60°C and 75% RH, an observed lactam content of between about 0.20 % to about 0.25 % (w/w) after storage 3 months at 40 °C and 75 % RH, and a predicted lactam content of between about 0.22 % to about 0.30 % (w/w). The tablets of Examples 6 and 7 exhibited an initial lactam content of between about 0.030 to about 0.040 % (w/w), a lactam content of between about 1.00 % to about 1.47 % (w/w) after storage for 14 days at 60°C and 75% RH, an observed lactam content of between about 0.75 % to about 0.95 % (w/w) after storage 3 months at 40 °C and 75 % RH, and a predicted lactam content of between about 0.73 % to about 1.05 % (w/w).

Further, the tablets of Example 3 and 4, which contain intragranular and extragranular hydroxypropylcellulose, were more stable than tablets of Example 5, which contain only intragranular hydroxypropylcellulose. Tablets of Examples 3 and 4 exhibited an initial lactam content of about 0.040 % (w/w), a lactam content of between about 0.17 % to about 0.21 % (w/w) after storage for 14 days at 60°C and 75% RH, an observed lactam content of between about 0.12 % to about 0.16 % (w/w) after storage 3 months at 40 °C and 75 % RH, and a predicted lactam content of between about 0.16 % to about 0.19 % (w/w). The tablets of Example 5 exhibited an initial lactam content of about 0.040 % (w/w), a lactam content of about 0.74 % (w/w) after storage for 14 days at 60°C and 75% RH, an observed lactam content of about 0.51 % (w/w) after storage 3 months at 40 °C and 75 % RH, and a predicted lactam content of about 0.55 % (w/w).

Tablets of Example 7, which contain intragranular and extragranular hydroxypropyl methylcellulose, were more stable than tablets of Example 6, which contain only intragranular hydroxypropyl methylcellulose. Tablets of Examples 7 exhibited an initial lactam content of about 0.030 % (w/w), a lactam content of about 1.00 % (w/w) after storage for 14 days at 60°C and 75% RH, an observed lactam content of about 0.75 % (w/w) after storage 3 months at 40 °C and 75 % RH, and a predicted lactam

content of about 0.73 % (w/w). The tablets of Example 6 exhibited an initial lactam content of between about 0.040 % (w/w), a lactam content of about 1.47 % (w/w) after storage for 14 days at 60 °C and 75% RH, an observed lactam content of about 0.94 % (w/w) after storage 3 months at 40 °C and 75 % RH, and a predicted lactam content of about 1.05 % (w/w).

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.

WE CLAIM:

1. A stable sustained-release tablet of gabapentin comprising:

an intragranular component comprising gabapentin and optionally one or more rate controlling polymers; and

an extragranular component comprising one or more rate-controlling polymers,

wherein lactam content does not exceed 0.4% by weight of gabapentin when the tablet is kept for about 3 months at about 40 °C and about 75% relative humidity.

2. The stable sustained-release tablet of claim 1, wherein the one or more rate-controlling polymers in the intragranular component and the one or more rate-controlling polymers in the extragranular component are the same or different.

3. The stable sustained-release tablet of claim 1, wherein the intragranular component comprises one or more rate controlling polymers.

4. The sustained-release tablet of claim 1, wherein the one or more rate-controlling polymers in the intragranular component and the extragranular component together comprise from about 5 % to about 80 % by weight of the tablet.

5. The sustained-release tablet of claim 4, wherein the one or more rate-controlling polymers in the intragranular component comprises from about 0 % to about 50 % by weight of the granules and the one or more rate-controlling polymers in the extragranular component comprises from about 5 % to about 80 % by weight of the tablet.

6. The sustained-release tablet of claim 1, wherein the rate-controlling polymers are selected from polyvinylpyrrolidone or derivatives thereof; a cellulosic polymer; a vinyl acetate copolymer; an alginate; xanthan gum; guar gum; starch; a starch-based polymer; polyethylene oxide; a methacrylic acid copolymer; a maleic anhydride/methyl vinyl ether copolymer or derivatives thereof; ethyl cellulose; cellulose acetate; a methacrylate; an acrylic acid polymer or copolymer; a high molecular weight polyvinyl alcohol; a wax; or mixtures thereof.

7. The sustained-release tablet of claim 5, wherein the cellulosic polymer is hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, methylcellulose or mixtures thereof.

8. The sustained-release tablet of claim 6, wherein the hydroxypropylmethylcellulose has a viscosity of about 100 cps to about 100,000 cps.

9. The sustained-release tablet of claim 7, wherein the hydroxypropylmethylcellulose has a viscosity of about 15,000 cps.

10. The sustained-release tablet of claim 7, wherein the hydroxypropylmethylcellulose has a viscosity of about 4000 cps.

11. The sustained-release tablet of claim 6, wherein hydroxypropylcellulose has a viscosity of about 7 cps to about 30,000 cps.

12. The sustained-release tablet of claim 10, wherein the hydroxypropylcellulose has viscosity of about 1000 cps to about 15000 cps.

13. The sustained-release tablet of claim 11, wherein the hydroxypropylcellulose has a viscosity of about 4000 cps.

14. The sustained-release tablet of claim 1, wherein the tablet further comprises one or more additional pharmaceutical excipients.

15. The sustained-release tablet of claim 13, wherein the one or more additional pharmaceutical excipients are selected from diluents, lubricants, glidants, binders or mixtures thereof.

16. The sustained-release tablet of claim 14, wherein the diluents are selected from powdered sugar, calcium phosphate, calcium sulphate, microcrystalline cellulose, lactose, mannitol, kaolin, dry starch, sorbitol or mixtures thereof.

17. The sustained-release tablet of claim 14, wherein the lubricants are selected from talc, stearic acid, vegetable oil, calcium stearate, zinc stearate, magnesium stearate or mixtures thereof.

18. The sustained-release tablet of claim 14, wherein the glidants are selected from talc, silicon dioxide, corn starch or mixtures thereof.

19. The sustained-release tablet of claim 14, wherein the binders are selected from polyvinylpyrrolidone, polyvinylpyrrolidone/vinylacetate copolymer, xanthan gum, guar gum, cellulose gums, gelatin, starch pregelatinized starch or mixtures thereof.

20. A process for preparing a stable sustained-release tablet of gabapentin comprising the steps of:

a. granulating a mixture comprising gabapentin, one or more pharmaceutical excipients and optionally one or more intragranular rate-controlling polymers with a granulating liquid to form an intragranular component;

b. drying, sizing and mixing the intragranular component with one or more extragranular rate-controlling polymers to form a blend, and

c. compressing the blend into a tablet.

21. The process of claim 19, wherein the optional one or more intrgranular rate-controlling polymers and the one or more extragranular rate-controlling polymers are the same or different.

22. The process of claim 19, wherein the intragranular component is prepared by wet granulation.

23. The process of claim 19, wherein the intragranular component is prepared by dry granulation.

24. The process of claim 22, wherein dry granulation is carried out by compacting or slugging.

25. A process for preparing a stable sustained-release tablet of gabapentin comprising the steps of:

a. mixing gabapentin, one or more pharmaceutical excipients and optionally one or more intragranular rate-controlling polymers to form a mixture;

b. compacting or slugging the mixture to form compacts or slugs;

c. sizing the compacts or slugs to form granules;

d. mixing the granules with one or more extragranular rate-controlling polymers to form a blend; and

e. compressing the blend into a tablet.

26. A method for treating epilepsy or post herpetic neuralgia comprising administering to a patient in need thereof a stable sustained-release tablet of gabapentin comprising:

an intragranular component comprising a therapeutically effective amount of gabapentin and optionally one or more rate controlling polymers; and

an extragranular component comprising one or more rate-controlling polymers,

wherein lactam content does not exceed 0.4% by weight of gabapentin when the tablet when kept for about 3 months at about 40 °C and about 75% relative humidity.

27. A tablet prepared by a process comprising the steps of:

a. granulating a mixture comprising gabapentin, one or more pharmaceutical excipients and optionally one or more intragranular rate-controlling polymers with a granulating liquid to form an intragranular component;

b. drying, sizing and mixing the intragranular component with one or more extragranular rate-controlling polymers to form a blend, and

c. compressing the blend into a tablet.

28. A tablet prepared by a process comprising the steps of:

a. mixing gabapentin, one or more pharmaceutical excipients and optionally one or more intragranular rate-controlling polymers to form a mixture;

b. compacting or slugging the mixture to form compacts or slugs;

c. sizing the compacts or slugs to form granules;

d. mixing the granules with one or more extragranular rate-controlling polymers to form a blend; and

e. compressing the blend into a tablet.