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(54) Title: STABILIZED DESMOPRESSIN

(57) Abstract: The invention is related to a pharmaceutical composition comprising an active ingredient and a stabilizing agent, wherein the active ingredient is desmopressin or a pharmaceutical acceptable salt thereof, and wherein the stabilizing agent is at least one gum, the use of one or more gums to increase the stability of a pharmaceutical composition comprising desmopressin or a pharmaceutical acceptable salt thereof as an active ingredient against denaturation, a method for preparing an orally disintegrating film comprising desmopressin or a pharmaceutically acceptable salt thereof as well as an orally disintegrating film obtainable thereby.

STABILIZED DESMOPRESSIN

FIELD OF THE INVENTION

[01] The present invention relates to pharmaceutical compositions comprising desmopressin or a pharmaceutically acceptable salt thereof as an active ingredient, wherein the desmopressin or pharmaceutically acceptable salt thereof is stabilized in the pharmaceutical composition, to methods for stabilizing desmopressin or a pharmaceutically acceptable salt thereof in a composition, to methods for preparing orally disintegrating films comprising desmopressin or a pharmaceutically acceptable salt thereof as well as to orally disintegrating films obtainable thereby.

BACKGROUND OF THE INVENTION

[02] Desmopressin is a synthetic analogue of the natural antidiuretic hormone vasopressin.

[03] Unlike vasopressin, desmopressin has no vasopressor activity, but only has antidiuretic activity. The selective antidiuretic activity is due to its ability to bind to V-2 receptors only and not to V-1 receptors. V-2 receptors are G-protein coupled receptors present in the collecting ducts of the kidney and are responsible for the promotion of water reabsorption via stimulation of cyclic AMP production. Desmopressin is effective in treatment of various urinary disorders, such as, but not limited to diabetes insipidus, incontinence, enuresis and nocturia, and dysfunctions of the coagulative system. In particular, desmopressin is useful in abnormal too frequent urination, particularly nocturnal polyuria, (passing of large volumes of urine at night but normal amounts during the day) which is the main cause of primary nocturnal enuresis (involuntary passage of urine during sleep) and nocturia (the complaint that the individual has to wake at night one or more times for urination).

[04] Most of the existing medicines used in the treatment of nocturnal enuresis and nocturnal polyuria are taken with water. Accordingly, there is a continuous need for further pharmaceutical preparations for treating urinary disorders such as nocturnal enuresis and nocturnal polyuria, which minimize the intake of water.

[05] Preparation of medications that will avoid the intake of water such as film preparations requires methods of manufacturing using relatively high temperatures, in particular during drying of the formulation to prepare the film. This may create drawbacks for the stability of the active agent desmopressin. Desmopressin (*1-desamino-8-D-arginine vasopressin*) is a peptide containing nine amino acids. Peptides generally tend to denature, i.e. lose their native state structure when for example external stress(es) is applied, when brought into contact with a compound(s) such as a strong acid or base, a concentrated inorganic salt, or an organic solvent (e.g., alcohol or chloroform), or e.g. when exposed to radiation or heat. Therefore, desmopressin is vulnerable to instability during and/or after medicine preparation, because of its tendency to denature, in particular due to thermal denaturation.

[06] Thus, there is a need for a desmopressin formulation that does not require water-intake and that is stable during processing, distribution, storage and preservation, and a method for the preparation thereof.

SUMMARY OF THE INVENTION

[07] The subject invention provides a pharmaceutical composition comprising an active ingredient and a stabilizing agent, wherein the active ingredient is desmopressin or a pharmaceutically acceptable salt thereof, and wherein the stabilizing agent is at least one gum.

[08] The subject invention further provides for the use of one or more gums to increase the stability of a pharmaceutical composition comprising desmopressin or a pharmaceutically

acceptable salt thereof as an active ingredient against denaturation, as a result of e.g. application of external stress(es) or contact with a compound(s) such as but not limited to a strong acid or base, a concentrated inorganic salt, or an organic solvent, or exposure to radiation or heat.

[09] The subject invention also provides for a method for preparing an orally disintegrating film, comprising adding at least one gum to a solution comprising desmopressin or a pharmaceutically acceptable salt thereof as an active ingredient and water as the only solvent, spreading the solution onto a support and drying the spread solution to prepare an orally disintegrating film.

[10] Finally, the subject invention provides for an orally disintegrating film obtainable by the above method.

DETAILED DESCRIPTION OF THE INVENTION

[11] The subject invention provides for a pharmaceutical composition comprising an active ingredient and a stabilizing agent, wherein the active ingredient is desmopressin or a pharmaceutically acceptable salt thereof, and wherein the stabilizing agent is at least one gum.

[12] In one embodiment, the pharmaceutically acceptable salt of desmopressin is desmopressin acetate.

[13] “Gum” as used herein should be understood to refer to hydrophilic materials that are polymers composed of heteropolysaccharides with high viscosity even at a low concentration, and are bound to water to form a viscous solution or a gel. The gum is used as a stabilizing agent for desmopressin or a pharmaceutically acceptable salt thereof. Non-limiting examples of ‘gums’ which can be used in the present invention are galactomannan gum (including acacia gum, locust bean gum, tara gum, and guar gum), carrageenan gum, xanthan gum, tragacanth gum, agar, quince seed gum, karaya gum, arabic gum, and gellan gum.

[14] In a preferred embodiment, the gum is xanthan gum.

[15] In a preferred embodiment, the composition does not substantially comprise additional stabilizing agents other than gum(s). As used herein, the term "not substantially comprise" means that the amount of additional stabilizing agents other than gum(s) is 10% (w/w) or less, 5% (w/w) or less, 4% (w/w) or less, 3% (w/w) or less, 2% (w/w) or less, 1% (w/w) or less, 0.5% (w/w) or less, and more preferably 0.1% (w/w) or less based on the total weight of all stabilizing agents used. In other words, the at least one gum constitutes at least 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9% by weight based on the total weight of all stabilizing agents used.

[16] The pharmaceutical composition may be administered for treating or preventing various urinary disorders such as diabetes insipidus, incontinence, enuresis and nocturia, and dysfunctions of the coagulative system, in particular nocturnal enuresis or nocturnal polyuria.

[17] It is envisaged that the pharmaceutical composition provides for increased stability of desmopressin or a pharmaceutically acceptable salt thereof against denaturation during application of external stress(es), contact with a compound(s) such as but not limited to a strong acid or base, a concentrated inorganic salt or an organic solvent, or when exposed to radiation or heat.

[18] It is envisaged that the pharmaceutical composition will provide increased stability of desmopressin or a pharmaceutically acceptable salt thereof against thermal denaturation, in particular against thermal denaturation during drying, during distribution, during storage and/or during preservation under normal conditions, meaning, in the context of this application, room temperature (15 – 25°C) and 60% relative humidity.

[19] The present invention further provides for the use of one or more gums to increase the stability of a pharmaceutical composition comprising desmopressin or a pharmaceutically acceptable salt thereof as an active ingredient against e.g. denaturation by application of

external stress(es), contact with a compound(s) such as, but not limited to, a strong acid or base, a concentrated inorganic salt, an organic solvent, or exposure to radiation or heat, in particular against thermal denaturation, more in particular against thermal denaturation during drying at a temperature of about 80°C for about 30 minutes or during at least 6 weeks distribution, storage and/or preservation under normal conditions.

[20] The subject invention further provides a method for preparing an orally disintegrating film, comprising adding at least one gum to a solution comprising desmopressin or a pharmaceutically acceptable salt thereof as an active ingredient and water as the only solvent, spreading the solution onto a support and drying the spread solution to prepare an orally disintegrating film.

[21] The solution used for the preparation of an orally disintegrating desmopressin film of the subject invention contains water as the sole solvent, thereby restricting the use of an organic solvent that may remain in a medicine to be administered to patients and may cause safety problems.

[22] Generally, the use of water as the sole solvent requires drying for a long duration under high-temperature conditions, as compared with the use of an organic solvent. For peptides such as desmopressin, such long duration high temperature conditions may result in deterioration of the composition's stability due to denaturation. In the present invention, this problem has been overcome by the addition of at least one gum, thereby concomitantly also obliviating the need for the use of (toxic) organic solvents in the production process.

[23] In the present invention, the preparation solution of an orally disintegrating film, after having being spread on a support, is preferably dried at a temperature of 100°C or less, 90°C or less, 80°C or less, preferably at about 80°C. For drying, time periods of 100 minutes or less, 50 minutes or less, 30 minutes or less, 20 minutes or less, more preferably 15 minutes or less have been proven to be appropriate so as to minimize the stability deterioration of desmopressin or a pharmaceutically acceptable salt thereof.

[24] In other embodiments, the preparation solution of an orally disintegrating film is preferably dried at a temperature of 100 °C or less for about 30 minutes, at a temperature of 90 °C or less for about 30 minutes, at a temperature of 100 °C or less for about 15 minutes, at a temperature of 90 °C or less for about 15 minutes, at a temperature of about 80℃ for about 30 minutes or at a temperature of about 80℃ for about 15 minutes so as to minimize the stability deterioration of desmopressin or a pharmaceutically acceptable salt thereof.

[25] Further, the present invention provides an orally disintegrating film prepared by the above-mentioned method. Particularly, the present invention provides an orally disintegrating film, comprising desmopressin or a pharmaceutically acceptable salt thereof as an active ingredient, in which a gum is used as a stabilizing agent for desmopressin.

[26] In the present invention, the thickness of the orally disintegrating film may be controlled by a person having ordinary skill, but is preferably controlled to be 80 μm or less so as to minimize the drying time and obtain the physical stability of the film.

[27] Thus, the present invention demonstrates that the use of one or more gums is specifically beneficial to increase the stability of a pharmaceutical composition comprising desmopressin or a pharmaceutically acceptable salt thereof as an active ingredient. In other words, the one or more gums are used as a stabilizing agent for stabilizing desmopressin or a pharmaceutically acceptable salt thereof against e.g. denaturation by application of external stress(es), contact with a compound(s) such as, but not limited to, a strong acid or base, a concentrated inorganic salt, or an organic solvent, or exposure to e.g. radiation or heat. In particular, the one or more gums are used as a stabilizing agent for stabilizing desmopressin or a pharmaceutically acceptable salt thereof against thermal denaturation.

[28] “Thermal denaturation” as used herein should be understood to refer to desmopressin or a pharmaceutically acceptable salt thereof being denatured by heat during

either the manufacturing process (e.g. during drying) of the pharmaceutical composition as well as under distribution, storage and preservation conditions. The pharmaceutical composition is thus stabilized against thermal denaturation e.g. during drying at a temperatures of 100℃ or less, 90℃ or less, 80℃ or less for 100 minutes or less, 50 minutes or less, 30 minutes or less, 20 minutes or less, or 15 minutes or less. The pharmaceutical composition is also stabilized against thermal denaturation during at least 6 weeks, at least 4 weeks, at least 3 weeks or at least 2 weeks of distribution, storage and/or preservation under normal conditions.

[29] In the present invention, the gum can effectively stabilize desmopressin or pharmaceutically acceptable salts thereof by the use of a small amount, compared to the amounts of gum(s) when used as e.g. thickening agents in pharmaceutical compositions. The weight ratio of desmopressin or a pharmaceutically acceptable salt thereof and the gum may range from 10:1 to 1:50, preferably from 5:1 to 1:30, more preferably from 3:1 to 1:10, most preferably from 1:1 to 1:2. When the gum is used in an amount less than the weight ratio range, desmopressin or a pharmaceutically acceptable salt thereof cannot be sufficiently stabilized. When the gum is used in an excessive amount higher than the weight ratio range, the viscosity becomes too high and it is difficult to obtain fluidity for several purposes, particularly during the manufacturing process.

[30] In the present invention, preferably, the pharmaceutical composition comprises about 0.1 to 0.5 percent by weight of desmopressin or a pharmaceutical acceptable salt thereof, and about 0.05 to 5 percent by weight of gum(s). The term 'pharmaceutically acceptable salt' as used herein refers to any organic or inorganic addition salts which are non-toxic and have an effective function harmless to the patients, so side effects attributed to the salts do not deteriorate the beneficial efficacy of desmopressin. For example, in order to form such a salt, organic acids and inorganic acids as a free acid, or non-toxic salts may be used. Examples of the inorganic acids may include hydrochloric acid, phosphoric acid,

sulfuric acid, nitric acid, and tartaric acid. Examples of the organic acids may include methanesulfonic acid, p-toluenesulfonic acid, acetic acid, trifluoroacetic acid, maleic acid, succinic acid, oxalic acid, benzoic acid, tartaric acid, fumaric acid, mandelic acid, propionic acid, citric acid, lactic acid, glycollic acid, gluconic acid, galacturonic acid, glutamic acid, glutaric acid, glucuronic acid, aspartic acid, ascorbic acid, carbonic acid, vanillic acid, and hydroiodic acid. Among these, acetic acid is preferably used. The acid addition salts may be prepared according to any conventional method, for example, by dissolving a compound in excessive amounts of an aqueous solution of acid, and precipitating the resulting salt in a water-miscible organic solvent such as methanol, ethanol, acetone, and acetonitrile. Examples of the non-toxic salts may include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogen phosphate, dihydrogen phosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, fluoride, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutylate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexane-1,6-dioate, benzoate, chlorobenzoate, methyl benzoate, dinitro benzoate, hydroxybenzoate, methoxy benzoate phthalate, terephthalate, benzene sulfonate, toluene sulfonate, chlorobenzene sulfonate, xylene sulfonate, phenyl acetate, phenyl propionate, phenyl butyrate, citrate, lactate, beta-hydroxybutyrate, glycolate, malate, tartrate, methane sulfonate, propane sulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, and mandelate.

[31] The pharmaceutical composition according to the present invention comprises desmopressin or a pharmaceutically acceptable salt thereof as an active ingredient, and therefore, can be used in the treatment or prevention of diseases, symptoms, and disorders that need the pharmacological effect of desmopressin or a pharmaceutically acceptable salt thereof, for example, nocturnal enuresis or nocturnal polyuria.

[32] The term ”treatment” as used herein refers to any actions that improve or favorably modify diseases, disorders and symptoms thereof by the administration of the

pharmaceutical composition. Also, the term 'treatment' includes the meaning of 'prevention' broadly, so the term 'prevention' refers to any actions that inhibit diseases, disorders and symptoms thereof or suppress occurrence thereof.

[33] The pharmaceutical composition according to the present invention may further comprise pharmaceutically acceptable carriers which are conventionally added to a pharmaceutical composition. The pharmaceutically acceptable carriers may include but are not limited to additives such as fillers, pH adjusting agents, protecting agents, wicking agents, diluents, disintegrating agents, binders, lubricants, emulsifiers, non-effervescent disintegrants, effervescent disintegrants, surfactants, anti-oxidants, wetting agents, taste-masking agents, preservatives and/or suspending agents. If necessary, sweetening agents, flavors, coloring agents and/or printing pigment colours may be further added.

[34] When the pharmaceutical composition of the present invention is used in the treatment of urinary disorders such as nocturnal enuresis, besides desmopressin or a pharmaceutically acceptable salt thereof, other drugs may concomitantly be used unless deteriorating the object of the present invention. For example, at least one drug selected from the non-limiting examples consisting of antidiuretic hormone, tolterodine, tamsulosine, amitriphthaline, and a combination thereof may optionally be further used.

[35] The pharmaceutical composition according to the present invention is formulated for oral administration. The formulation for oral administration may take various forms such as tablet, film, suspension, granule, gel, pill, tincture, decoction, infusion, spirit, fluid extract, elixir, extract, syrup, powder, aromatic water, and lemonade. Also, the tablet may take various forms such as an orally disintegrating tablet, a mucoadhesive tablet, a dispersible tablet, a sublingual tablet, a buccal tablet, a chewable tablet, a dispensing tablet, a mulitilayered tablet, a press-coated tablet, an effervescent tablet, and a solution tablet. If necessary, the various tablets may also be variously modified by a person having ordinary skill. More preferably, for administration without water intake, a liquid form or an orally

disintegrating formulation, for example, orally dispersing (dissolving) formulations, such as an orally dissolving film, an orally disintegrating tablet, a suspension, a suspending tablet, an immediate release dissolving tablet, an orally disintegrating granule, an orally disintegrating troche, a sublingual tablet, a powder, and/or a chewable tablet may be used.

[36] Considering several objects, the pharmaceutical composition according to the present invention is preferably formulated in the form of an orally dissolving film. The terms “orally dissolving film”, “film”, ”strip” and “orally disintegrating film” are used interchangeably herein and should be understood to be administered by placing it on the tongue, under the tongue, in the oral cavity, or any other mucosal sublingual parts.

[37] The orally disintegrating film of the present invention dissolves in less than 30 seconds i.e. fulfills the respective criteria for such type of medication both in the U.S. and Europe.

[38] According to the present invention, the addition of gum(s) can thus effectively stabilize desmopressin or a pharmaceutically acceptable salt thereof to allow formulation in the form of a film, in particular an orally disintegrating film, thereby solving the need for water intake, and also allow for drying of the film preparation solution in which water is used as the sole solvent.

EXAMPLES

[39] The invention is further described in the following examples, which are not in any way intended to limit the scope of the inventions as claimed.

Preparation Example

Preparation of a Film Formulation comprising Desmopressin as an Active Ingredient

[40] A film formulation which has an increased stability against denaturation of desmopressin was prepared as follows:

[41] A gum as well as further excipients (as specified in nature and amounts below in the Examples) were added to water and stirred for dissolution and dispersion, followed by homogenization using a homogenizer (Ultra Turrax T-25, IKA, 5000 rpm). Thereto, desmopressin acetate was added and dissolved, followed by homogenization again using the same homogenizer. The resulting film-preparation solution was degassed under vacuum conditions, and coated onto a polyethylene terephthalate (PET) film. The film was dried (under conditions as specified below in the Examples) to obtain a desmopressin-containing film formulation having a thickness of 80㎛.

Analytical Tests

[42] The analytical tests used in the following Examples are based on <Desmopressin Acetate, USP 35> and are described in detail as follows:

Total Impurities (Examples 1, 2, 3) and Assay (Example 1)

Test solution – Examples 1, 2, 3

[43] A film prepared according to the Preparation Example, equivalent to 1 mg of desmopressin acetate, was put in a 10 ml volume flask. It was mixed with the mobile phase as listed for the HPLC conditions hereinunder until the solution reached the marking for 10 ml. The solution was put into a centrifuge tube, and then centrifuged for 20 minutes. The solution was filtered with 0.2 µm filter (hydrophilic polytetrafluoroethylen (PTFE)). The completion of these steps resulted in the test solution (0.1 mg/ml).

Excipient solution – Examples 2, 3

[44] The amount of each excipient (HPC, TiO_2, gums) in the film used for preparation of

test solution was put in a 10 ml volume flask. The mobile phase as listed for the HPLC conditions hereinunder was poured into the flask until the solution reached the marking for 10 ml. The solution was put into the centrifuge tube and then centrifuged for 20 minutes. The solution was filtered with 0.2 µm filter (hydrophilic PTFE). The completion of these steps resulted in the excipient solution. This solution was used for identification of peaks originating from excipients which might show on the chromatograms. These peaks have to be distinguished from the peaks of the active ingredient and the impurities originating from denaturation thereof.

Blank – Examples 1, 2, 3

[45] The mobile phase alone is used as a blank test solution to identify characteristics thereof to distinguish from other peaks on the chromatograms.

Standard solution - for Assay analysis – Example 1

[46] 20 mg of desmopressin acetate was taken accurately, and put in a 200 ml volume flask with mobile phase. The solution was sonicated, and then stirred for dissolution (0.1 mg/ml).

Calculation of Assay and Total Impurities

1. Assay

$$\text{Assay}(\%) = \frac{At}{As} \times \frac{Cs}{Ct} \times P$$

At : Area response of desmopressin in test sample solution

As : Area response of desmopressin in standard sample solution

Ct : Desmopressin concentration of test sample solution

Cs : Desmopressin concentration of standard sample solution

P : Purity of desmopressin acetate standard (%)

2. Total Impurities

Total Impurities = Sum of Individual Impurities

$$\text{Individual Impurity(\%)} = \frac{Ai}{At} \times 100$$

Ai : Area response of impurity in test sample solution

At : Area response of desmopressin in test sample solution

* The peaks from the blank solution and the excipient solution were excluded from the calculation of the area response of the impurity.

HPLC conditions

- Detector : UV (220 nm)
- Column : ODS (L1), 250 x 4.6mm, 5 µm

  (Kromasil 100-5-C18, 250 x 4.6 mm)
- Column oven : 30℃
- Flow rate : 1.0 ml/min.
- Injection volume : 100 µl
- Mobile phase

  Buffer* : Acetonitrile (78 : 22)

- Run time : 50 min.

* Buffer solution : 3.4 g of monobasic potassium phosphate and 2.0 g of sodium 1-heptanesulfonic acid was dissolved in 1000 ml of water. The pH was adjusted to 4.50±0.05 with phosphoric acid or sodium hydroxide, as needed and passed through a filter having a porosity of 0.45 μm.

LOD (Examples 1,2)

[47] 0.5 g of the film prepared as described above in the Preparation Example was tested as follows:

- A glass bottle was dried in 105℃ chamber for 1 hour and then cooled down for 30 minutes in the desiccator (room temperature).

- The cooled glass bottle from the desiccator was weighed. The film sample was then rolled or folded and then, without undue delay, put in a glass bottle in standing position. The glass bottle with the sample was weighed accurately.

- The glass bottle with the film sample was incubated in the 105℃ chamber for 4 hours.

- After 4 hours, the glass bottle was cooled down for 30 minutes in the desiccator (room temperature).

- The cooled glass bottle was then weighed without undue delay.

- To calculate the LOD value, the reduced weight of the film sample was divided by the weight of the first film sample.

Example 1

Determination of the Conditions for the Film Drying

[48] The film-preparation solutions were prepared by the same method as described in the Preparation Example, with the components and amounts as given in Table 1. The resulting film-preparation solutions were degassed under vacuum conditions, and coated on a PET film. The films were dried under different drying conditions (Temperature, Moving speed, Air flow rate) (See Table 2).

Table 1

Composition	Amount (%)
Desmopressin acetate	0.25
Xanthan gum	0.25
Titanium dioxide	10.00
Hydroxypropyl cellulose (HPC)	89.50
Water	Q.S.

Table 2

Test No.	Drying condition		Retention time in Dryer (min.)	Zone within drying chamber			
				1	2	3	4
1	Speed(m/min)	Temperature(℃)	10.0	80	80	85	90
	0.8	Air flow rate(RPM)		1000	1200	1400	1700
2	Speed(m/min)	Temperature(℃)	10.0	80	80	85	100
	0.8	Air flow rate(RPM)		1000	1200	1400	1700
3	Speed(m/min)	Temperature(℃)	10.0	80	80	100	100
	0.8	Air flow rate(RPM)		1000	1200	1400	1700
4	Speed(m/min)	Temperature(℃)	13.2	80	80	100	100
	0.6	Air flow rate(RPM)		1000	1200	1400	1700
5	Speed(m/min)	Temperature(℃)	10.0	80	80	100	110
	0.8	Air flow rate(RPM)		1000	1200	1200	1700
6	Speed(m/min)	Temperature(℃)	13.2	80	80	110	110
	0.6	Air flow rate(RPM)		1000	1200	1200	1700
7	Speed(m/min)	Temperature(℃)	13.2	80	80	100	100
	0.6	Air flow rate(RPM)		1200	1400	1600	1700

RPM : revolutions per minute

[49] The sampled film samples (300mm X 300mm) at each set of drying conditions (Table 2) were packed in multi-layer aluminium foil, and sealed. After 6 hours, the tests namely Assay, Loss on Drying (LOD) and Total Impurities, for each sample were carried out. Assay (%) determines the amount of desmopressin maintained after film drying. Total impurities (%) determines the amount of impurities from desmopressin measured after film drying. Loss on Drying (%) is the value to measure the amount of volatile matters (in particular, water) in a film after the film is dried. For example, the LOD of 8.5 (%) of Test

sample no. 1 in Table 3 indicates that the loss in weight is 8.5% of the film. The results of the tests are shown in Table 3.

Table 3

Test No.	Retention time in a Dryer (min.)	Min./Max. temperature (℃)	Assay(%)	LOD(%)	Total Impurities(%)	Result
1	**10.0**	**80/90**	**99.5**	8.5	0.61	**Good**
2	**10.0**	**80/100**	**97.8**	7.9	0.73	**Good**
3	**10.0**	**80/100**	**100.0**	8.0	0.77	**Good**
4	**13.2**	**80/100**	**102.4**	8.1	0.74	**Good**
5	10.0	80/110	95.6	8.2	0.75	Poor
6	13.2	80/110	86.0	6.4	1.04	Poor
7	**13.2**	**80/100**	**99.2**	6.9	0.67	**Good**

[50] The overall result was deemed to be “Good” when the results of all three tests met the following criteria: Assay: 97.0 – 103.0%; LOD not more than (NMT) 10%; Total Impurities: NMT 1.0%. When at least one of the test results did not meet the respective criterion, the overall result was deemed to be “Poor”.

[51] Test Nos. 1 to 4 and 7 satisfied all of three conditions.

[52] In Test Nos. 5 and 6, the LOD value was lower than 10.0%. In addition, Total Impurities (%) was also not lower than 1.0% in Test No. 6 but lower than 1.0% in Test No. 5, . However, in Test Nos. 5 and 6, the Assay value was out of the range of 97.0% to103.0% so that the overall result for both Test No. 5 and 6 was “Poor”.

[53] From the above results, it was concluded that desmopressin acetate films cannot maintain stability if being dried at the highest temperature of 110℃ for 10 minutes or more.

Example 2

The Stabilizing Effect of Gum(s)

[54] The film was prepared according to the method as described in the Preparation Example with the components and amounts as given in Table 4. The film was dried at 80°C for 30 minutes.

Table 4

Composition (%)			Example							
		control	1	2	3	4	5	6	7	8
Desmopressin acetate		0.25								
Xanthan gum		-	0.025	0.050	0.083	0.250	0.500	2.500	7.500	12.500
Titanium dioxide		10.0								
Hydroxypropyl cellulose (HPC)		Q.S.								
Water		Q.S.								
Total (as solid)		to 100.0 %								
Viscosity of solution		3,000 - 4,000 cp	3,000 - 4,000 cp	3,000 - 4,000 cp	3,000 - 4,000 cp	3,000 - 4,000 cp	3,000 - 4,000 cp	7,000 - 8,000 cp	8,000 - 9,000 cp	> 10,000 cp
Loss on drying (%)		4.9	4.2	5.0	4.3	5.2	4.7	4.5	5.1	5.3
Total impurities (%)	Before drying	≤ 0.3								
	Initial (after drying)	≤ 0.7	≤ 0.7	≤ 0.7	≤ 0.6	≤ 0.4	≤ 0.3	≤ 0.3	≤ 0.3	≤ 0.3
	2 weeks after drying (Accelerated conditions)	≤ 1.5	≤ 1.0	≤ 0.8	≤ 0.8	≤ 0.5	≤ 0.5	≤ 0.3	≤ 0.3	≤ 0.3
	4 weeks after drying (Accelerated conditions)	≥ 3.0	≤ 1.4	≤ 1.0	≤ 0.9	≤ 0.6	≤ 0.6	≤ 0.4	≤ 0.3	≤ 0.3

[55] Viscosity of solution was measured using a Brookfield viscometer. The results of the stability measurements are shown as Total Impurities (%). Total Impurities (%) determines

the total amount of impurities of desmopressin measured after 2 – 4 weeks under accelerated conditions (40±2°C, Relative Humidity 75±5%).

[56] The standard deviation of the LOD values was ±0.5% and there was no significant difference between the test groups.

[57] As a result, as can be seen in Table 4, the gum, in this example xanthan gum, as a stabilizer, resulted in a significant reduction of the Total Impurities under accelerated storage conditions as well as immediately after film drying, compared to an identical composition without any gum (control), over the whole weight ratio range of desmopressin acetate to gum of 10:1 to 1:50. The strongest improvement in stability for very small amounts of gum added (columns 1 to 4) was seen for a weight ratio of 1:1, whereas the improvement in stability for further addition of gum (columns 5 to 8) was also existent.

Example 3

The Stabilizing Effect of Different Kinds of Gum(s)

[58] The film was prepared according to the method as described in the Preparation Example, with the components and amounts as given in Table 5. The film was dried at 80°C for 30 minutes.

Table 5

Ingredients		(%)
Desmopressin Acetate		0.25
TiO_2		10
HPC		89.5
gums	Xanthan gum	0.25
	Arabic gum	
	Agar	
	Carrageenan	
Water		To 100
Total dried weight		100

Ingredients		(%)
Desmopressin Acetate		0.25
TiO_2		10
HPC		77.26
gums	Xanthan gum	12.49
	Arabic gum	
	Agar	
	Carrageenan	
Water		To 100
Total dried weight		100

[59] The results of the stability measurements are shown as Total Impurities (%) (see Table 6). Total Impurities (%) determines the total amount of impurities of desmopressin measured after film drying ('Initial' in Table 6) and after 2 – 4 weeks under accelerated conditions (40±2℃C, Relative Humidity 75±5%).

[60] From the test results in Table 6, it can be seen that any kind of gum added showed a significant stabilizing effect compared to a composition without any gum added (column Control). In case that a high concentration of gum was used (weight ratio of desmopressin acetate (API) to gum of 1:50), an excellent stabilizing effect was shown, regardless of the kind of gum. However, in case that a low concentration of gum was used (weight ratio of 1:1), xanthan gum showed the most prominent stabilizing effect.

Table 6

API:Stabilizer	Control	1:1				1:50			
Stabilizer	Not added	Xanthan gum	Arabic gum	Agar	Carrageenan	Xanthan gum	Arabic gum	Agar	Carrageenan
Before drying	≤0.3	≤0.3	≤0.3	≤0.3	≤0.3	≤0.3	≤0.3	≤0.3	≤0.3
Initial (After drying)	≤0.7	≤0.3	≤0.4	≤0.4	≤0.4	≤0.3	≤0.3	≤0.3	≤0.3
2 weeks after drying (Accelerated conditions)	≤2.0	≤0.5	≤0.7	≤1.0	≤0.8	≤0.3	≤0.3	≤0.4	≤0.4
4 weeks after drying (Accelerated conditions)	≥3.0	≤0.6	≤2.0	≤2.0	≤2.0	≤0.3	≤0.5	≤0.6	≤0.5

CLAIMS

1. A pharmaceutical composition comprising an active ingredient and a stabilizing agent wherein the active ingredient is desmopressin or a pharmaceutically acceptable salt thereof, and wherein the stabilizing agent is at least one gum.
2. The pharmaceutical composition according to claim 1 for treating or preventing nocturnal enuresis or nocturnal polyuria.
3. The pharmaceutical composition according to claim 1 or 2, which is stabilized against denaturation.
4. The pharmaceutical composition according to claim 3, which is stabilized against thermal denaturation.
5. The pharmaceutical composition according to claim 4, which is stabilized against thermal denaturation during drying.
6. The pharmaceutical composition according to claim 4, which is stabilized against thermal denaturation during distribution, storage and/or preservation under normal conditions.
7. The pharmaceutical composition according to any of the preceding claims, wherein the pharmaceutically acceptable salt is desmopressin acetate.
8. The pharmaceutical composition according to any of the preceding claims, wherein the gum is xanthan gum.
9. The pharmaceutical composition according to any of the preceding claims, wherein the weight ratio of desmopressin or a pharmaceutically acceptable salt thereof and the gum(s) ranges from 10:1 to 1:50.
10. The pharmaceutical composition according to claim 9, wherein the weight ratio of desmopressin or a pharmaceutically acceptable salt thereof and the gum(s) ranges from 5:1 to 1:30.

11. The pharmaceutical composition according to claim 10, wherein the weight ratio of desmopressin or a pharmaceutically acceptable salt thereof and the gum(s) ranges from 3:1 to 1:10.

12. The pharmaceutical composition according to claim 11, wherein the weight ratio of desmopressin or a pharmaceutically acceptable salt thereof and the gum(s) ranges from 1:1 to 1:2.

13. The pharmaceutical composition according to any of claims 9 to 12, wherein the composition comprises about 0.1 to 0.5 percent by weight of desmopressin or a pharmaceutical acceptable salt thereof, and about 0.05 to 5 percent by weight of gum(s).

14. Use of one or more gums to increase the stability of a pharmaceutical composition comprising desmopressin or a pharmaceutically acceptable salt thereof as an active ingredient against denaturation.

15. Use according to claim 14, wherein the pharmaceutical composition is stabilized against thermal denaturation.

16. Use according to claim 15, wherein the pharmaceutical composition is stabilized against thermal denaturation during drying at a temperature of about 80°C for about 30 minutes or during at least 6 weeks distribution, storage and/or preservation under normal conditions.

17. A method for preparing an orally disintegrating film, comprising adding at least one gum to a solution comprising desmopressin or a pharmaceutically acceptable salt thereof as an active ingredient and water as the only solvent, spreading the solution onto a support and drying the spread solution to prepare an orally disintegrating film.

18. The method according to claim 17, wherein the drying is carried out at a temperature of 100°C or less.

19. The method according to claim 18, wherein the drying is carried out at a temperature

of about 80°C.

20. An orally disintegrating film obtainable by a method according to any one of claims 17 to 19.

21. The orally disintegrating film according to claim 20, which has a thickness of $80\mu m$ or less.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/063347

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K38/00 A61K47/36
ADD.

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)
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 practicable, search terms used)
EPO-Internal, EMBASE, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/083323 A2 (PANACEA BIOTEC LTD [IN]; SINGH AMARJIT [IN]; SINGH SARABJIT [IN]; PUTH) 26 July 2007 (2007-07-26) claims 4, 22 page 2, line 31 page 4, line 29 - page 5, line 2	1-8,14
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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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
9 September 2015	16/09/2015

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	PRAJAPATI VIPUL D ET AL: "Pharmaceutical applications of various natural gums, mucilages and their modified forms", CARBOHYDRATE POLYMERS, APPLIED SCIENCE PUBLISHERS, LTD. BARKING, GB, vol. 92, no. 2, 15 November 2012 (2012-11-15), pages 1685-1699, XP028972872, ISSN: 0144-8617, DOI: 10.1016/J.CARBPOL.2012.11.021 table 1 -----	

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