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(54) **Title:** TOPICAL PHARMACEUTICAL COMPOSITIONS COMPRISING NEBIVOLOL FOR THE TREATMENT OF DIABETIC WOUNDS

(57) **Abstract:** The present invention relates to a stable topical pharmaceutical composition of nebivolol for the treatment of diabetic wounds in a subject, wherein the time for complete wound closure (in days) after topical administration of the composition is less than or equal to that of the marketed product, becaplermin gel.



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TOPICAL PHARMACEUTICAL COMPOSITIONS COMPRISING NEBIVOLOL FOR THE TREATMENT OF DIABETIC WOUNDS

Field of the Invention

The present invention relates to a stable topical pharmaceutical composition of
5 nebivolol for the treatment of diabetic wounds in a subject, wherein the time for complete
wound closure (in days) after topical administration of the composition is less than or
equal to that of the marketed product, becaplermin gel.

Background of the Invention

Diabetes mellitus is a chronic metabolic disorder that results in slow
10 neovascularization and impaired diabetic wound healing. Diabetic wounds are
characterized by infection, ulceration, and destruction of deep tissues associated with
neurological anomalies and various degrees of peripheral vascular diseases, in particular
those of lower limbs which further progress into diabetic foot ulcers. The diabetic foot
ulcers are classified into grade 1 and grade 2 diabetic foot ulcers. Grade 1 is characterized
15 by the superficial ulceration of skin or subcutaneous tissue, while grade 2 is characterized
by ulcers extending into tendon, bone, or capsule.

The current treatment management strategies for diabetic wounds include
antibiotics and dressings in combination with glycemic control. The only approved
treatment available is in the form of a topical gel of recombinant human platelet derived
20 growth factor, Regranex[®] (becaplermin gel, 0.01%), which is indicated for the treatment
of diabetic foot ulcers. However, becaplermin is expensive and comes with a black box
warning for an increased rate of mortality secondary to malignancy. Hence, there is a
clear unmet need for safer alternative treatment options for diabetic wound management.

A topical delivery system is advantageous over systemic delivery because it
25 provides high local concentrations of the drug and respite from systemic toxic effects.

PCT Publication No. WO 2008/093356 discloses that the topical administration of
beta blockers is effective in the treatment of diabetic complications such as diabetic
wounds. It also discloses that diabetes results in increased aldose reductase activity in
diabetic patients which leads to diabetic complications such as diabetic wounds.
30 However, this publication discloses a study wherein nebivolol was found to be less
effective than other beta blockers in inhibiting aldose reductase activity.

Gulcan *et al.* discloses the administration of a topical cream comprising nebivolol for treatment of diabetic ulcers in rats (European Journal of Pharmaceutical Sciences 47(2), 451–455 (2012)). The drug was found to be more efficacious than the placebo.

The inventors have now found that the topical pharmaceutical compositions of
5 nebivolol of the present invention provide accelerated wound healing of diabetic wounds.

Summary of the Invention

There is provided a stable topical pharmaceutical composition of nebivolol for the treatment of diabetic wounds in a subject, wherein the composition provides a more accelerated wound closure of diabetic wounds than the marketed product, becaplermin gel.

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Detailed Description of the Invention

A first aspect of the present invention provides a stable topical pharmaceutical composition of nebivolol for the treatment of diabetic wounds in a subject, wherein the time for complete wound closure (in days) after topical administration of the composition is less than or equal to that of the marketed product, becaplermin.

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As used herein, the term “nebivolol” includes nebivolol and pharmaceutically acceptable salts thereof. The pharmaceutically acceptable salts include hydrochloride, hydrobromide, phosphate, sulphate, mesylate, besylate, tosylate, fumarate, malonate, malate, succinate, lactate, glycolate, maleate, citrate, and aspartate. In particular, the pharmaceutically acceptable salt is nebivolol hydrochloride. Nebivolol may be present in
20 hydrate or anhydrate forms. It may also be present in crystalline or amorphous forms. The amount of nebivolol may vary from about 0.01% w/w to about 50% w/w of the pharmaceutical composition. In particular, the amount of nebivolol may be present in the composition in the range of about 0.5% w/w to about 20% w/w of the composition.

The pharmaceutical composition of the present invention can be used for the
25 treatment of diabetic wounds, in particular grade 1 and grade 2 diabetic foot ulcers. This composition is intended to be used as an adjunct to standard wound management interventions consisting of initial complete sharp debridement and systemic treatment for wound-related infection, along with strict glycemic control.

As used herein, the term “complete wound closure” refers to the closure of a
30 wound that leaves no part of the wounded tissue exposed.

According to one embodiment of this aspect, the pharmaceutical composition provides 100% re-epithelialization of the wound.

The term “re-epithelialization,” as used herein, refers to a proliferation of epithelial cells over the wound bed, providing a cover for the new granulation tissue.

5 The composition of the present invention may be in the form of a cream, gel, powder, lotion, ointment, liniment, solution, suspension, paste, aerosol, or spray.

According to one embodiment of this aspect, the pharmaceutical composition of nebivolol may be applied topically once, twice, or thrice daily for one to three weeks.

10 According to another embodiment of this aspect, the topical composition is an ointment-based composition. In particular, the ointment-based composition comprises paraffin.

 According to another embodiment of this aspect, the topical composition is stable when exposed to 40°C/75% RH for a period of 3 months or more. Further, it is stable at room temperature for more than 1 year. In particular, the topical composition was found
15 to be stable when exposed to 40°C/75% RH for a period of 6 months.

 According to another embodiment of this aspect, the pH of the topical composition is less than 8. In particular, the pH of the topical composition is between 2.0 and 7.0.

 According to another embodiment of the above aspect, the topical pharmaceutical composition further comprises pharmaceutically acceptable excipients selected from the
20 group comprising viscosity enhancers, emollients, surfactants, preservatives, chelating agents, anti-oxidants, pH-adjusting agents, solvents, co-solvents, vehicles, and mixtures thereof.

 A second aspect of the present invention provides a stable topical pharmaceutical composition of nebivolol for the treatment of diabetic wounds in a subject, wherein the
25 pharmaceutical composition is prepared by a process comprising:

- i) dispersing nebivolol in a solvent to obtain a drug dispersion;
- ii) mixing other pharmaceutically acceptable excipients with the drug dispersion of step i) to obtain a mixture;
- iii) optionally, melting the mixture of step ii) to obtain a molten mixture;

iv) mixing the mixture of ii) or the molten mixture of step iii) with a vehicle to obtain the desired composition; and

v) filling the composition of step iv) into a suitable sized container.

Suitable viscosity enhancers are selected from the group comprising soft paraffin, aluminum stearate, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, cross-linked polyacrylate polymer, *e.g.*, Carbomer 980, glyceryl behenate, povidone, wool-fat, hydrogenated lanolin, beeswax, white wax, and mixtures thereof. These may be present in the composition in the range of about 0.1% w/w to about 40% w/w of the composition.

Suitable emollients are selected from the group comprising isopropyl myristate, medium chain triglycerides, myristic acid, palmitic acid, glyceryl linoleate, cyclomethicone, dimethicone, decyl oleate, stearic acid, and mixtures thereof. These may be present in the composition in the range of about 1% w/w to about 50% w/w of the composition.

Suitable surfactants are selected from the group comprising sorbitan monostearate, polyoxyethylene sorbitan monostearate, *e.g.*, Polysorbate 60 or Polysorbate 80, non-ethoxylated glyceryl monostearate, cetomacrogol, cetostearyl alcohol, cetearyl alcohol, sodium stearyl lactylate, lecithin, and mixtures thereof. These may be present in the composition in the range of about 0.1% w/w to about 20% w/w of the composition.

Suitable preservatives are selected from the group comprising methyl paraben, propyl paraben, benzyl alcohol, benzoic acid, sodium benzoate, chlorocresol, sorbic acid and its salts, phenylethyl alcohol, and mixtures thereof. These may be present in the composition in the range of about 0.01% w/w to about 5% w/w of the composition.

Suitable chelating agents are selected from the group comprising dimercaprol, ethylene diamine tetra acetic acid (EDTA), ethylene glycol tetra acetic acid, deferoxamine, alfa lipoic acid, and mixtures thereof. These may be present in the composition in the range of about 0.01% w/w to about 10% w/w of the composition.

Suitable antioxidants are selected from the group comprising sodium metabisulfite, butylated hydroxy toluene, butylated hydroxy anisole, propyl gallate, ethyl gallate, methyl gallate, ascorbic acid, tocopherol, and mixtures thereof. These may be present in the composition in the range of about 0.01% w/w to about 10% w/w of the composition.

Suitable pH-adjusting agents are selected from the group comprising citric acid, sodium citrate, acetic acid, sodium acetate, phosphoric acid, disodium orthophosphate, borax, sodium hydroxide, and sodium phosphate. These may be present in the composition in the range of about 0.01% w/w to about 10% w/w of the composition.

- 5 Suitable solvents are selected from the group comprising ethyl alcohol, isopropyl alcohol, acetone, and mixtures thereof. These may be present in the composition in the range of about 0.01% w/w to about 50% w/w of the composition.

- Suitable co-solvents are selected from the group comprising heavy liquid paraffin, water, propylene glycol, and various grades of polyethylene glycols, *e.g.*, polyethylene
10 glycol 400. These may be present in the range of about 20% w/w to about 80% w/w of the composition.

 Suitable vehicles are selected from the group comprising white soft paraffin, polyethylene glycol, purified water, and mixtures thereof. These may be present in the range of about 40% w/w to about 80% w/w of the composition.

- 15 The term “about,” as used herein, refers to any value which lies within the range defined by a variation of up to $\pm 10\%$ of the value.

- The following examples represent various embodiments according to the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible
20 without departing from the spirit and scope of the invention.

EXAMPLES

Example 1

Ingredients	Quantity (% w/w)
Nebivolol hydrochloride equivalent to nebivolol	5.00
Butylated hydroxy toluene	0.10
Butylated hydroxy anisole	0.10
Propyl paraben	0.05
Heavy liquid paraffin	25.00
Glyceryl behenate	5.00
White wax	2.00
White soft paraffin	q.s. to 100.00

Manufacturing process:

1. Glyceryl behenate, white wax, a portion of white soft paraffin, propyl paraben, butylated hydroxy toluene, and butylated hydroxy anisole were heated and then cooled to obtain a melted mixture.
- 5 2. Nebivolol hydrochloride was dispersed into heavy liquid paraffin to obtain a dispersion.
3. The dispersion of step 2 was mixed with the melted mixture of step 1.
4. The mixture of step 3 was mixed with the remaining white soft paraffin to obtain an ointment.
- 10 5. The ointment of step 4 was packed into suitable sized tubes.

Similarly, compositions comprising nebivolol in strengths of 10.00% w/w and 20.00% w/w of the composition were also prepared according to the procedure described above.

Irritation Potential Study

Irritation potential of the composition of the present invention was compared with placebo in a single dose dermal irritation study. A total of 7 young adult healthy male New Zealand White Rabbits (six rabbits for Example 1 and one rabbit for placebo) were used in this study. The fur of the rabbits was removed and 4 sites (2 treated and 2
20 untreated test sites) were identified. The skin was abraded (only on treated test sites) with a sterile needle 18 to 24 hours prior to the application of the composition of Example 1 and the placebo. 500 mg each of the composition of Example 1 and placebo was applied directly to the designated treated test sites created on either the right or left dorso-lateral trunk of the rabbits, each having a surface area of approximately 6 cm². The site was then
25 covered with a gauze patch which was held in place with the help of cotton crepe bandage. For the untreated test sites, only the gauze patch was applied.

All of the rabbits were examined for signs of erythema and edema, and the responses were recorded immediately and then after 24, 48, and 72 hours (±15 minutes) of the application. The evaluation of the irritation potential of the placebo and Example 1
30 was done against the untreated test site.

Based on the results of the study, the compositions of the present invention were found to be non-irritant.

Wound healing study

The time taken for the complete wound closure and percent re-epithelialization was studied in Wistar rats. The rats were distributed into 5 groups: the non-diabetic control rats (group 1), diabetic control rats (group 2), placebo for Example 1 (group 3), Regranex[®] (group 4), and Example 1 (group 5). The complete wound closure study consisted of 7 rats in each group, while the percent re-epithelialization study consisted of 5 rats in each group.

After the acclimatization of all the rats to laboratory conditions, the rats of groups 2, 3, 4, and 5 were administered streptozocin (STZ) via intraperitoneal injection at a dose of 50 mg/kg body weight for three alternate days. After 10 days following the last injection, the blood glucose levels of the rats were measured, and only the rats showing blood glucose values >300 mg/dL were further considered for the wound healing study.

The rats were anaesthetized by administering an intraperitoneal injection of a mixture of xylazine (dose 5 mg/kg body weight) and ketamine (dose 40 mg/kg body weight) which was prepared in sterile water for injection. In these fully anesthetized rats, a circular area (approximately 15 mm diameter) was marked on the shaved dorsal thoracic region. A full skin thickness wound was created by removing the entire skin layer from the marked area with sterile surgical scissors and forceps. The day of wound creation was considered as day 0. From the next day (*i.e.*, approximately 24 hours $\pm$ 2 hours after wound creation), the compositions were applied twice daily in groups 3, 4, and 5 with the help of a sterile stainless steel spatula. The marketed formulation Regranex[®] (becaplermin 0.01% gel) has been used as a reference standard.

The time (in days) for wound closure was recorded. A histomorphometric analysis was carried out to determine the percent of re-epithelialization on day 8 and day 15 using Leica[®] QWin image analysis software.

Table 1: Time (in days) for wound closure in diabetic rat

Group (N=7)	1	2	3	4	5
Time in days (Mean $\pm$ SD)	15.6 $\pm$ 1.27	19.3 $\pm$ 4.54	19.6 $\pm$ 6.77	16.3 $\pm$ 1.50	14.3 $\pm$ 0.58

Table 2: Percent re-epithelialization on day 8 and day 15

Day 8					
Group	1	2	3	4	5
N	5	4	5	5	4
Percent re-epithelialization (Mean $\pm$ SD)	29.92 $\pm$ 11.12	31.58 $\pm$ 6.11	27.09 $\pm$ 11.01	26.50 $\pm$ 18.97	14.79 $\pm$ 6.40
Day 15					
N	5	4	4	5	3
Percent re-epithelialization (Mean $\pm$ SD)	100.00 $\pm$ 0.00	90.92 $\pm$ 18.16	92.66 $\pm$ 9.87	100.00 $\pm$ 0.00	100.00 $\pm$ 0.00

Regranex[®] gel (group 4) showed comparable results with that of the non-diabetic control (group 1) in re-epithelialization of the wound. The Example 1 formulation (group 5) was found to be comparable with Regranex[®] gel and the non-diabetic control in re-epithelialization and complete closure of the wound.

Stability Testing

The ointments obtained from Example 1, after being packed in lami tubes, were subjected to stability testing at room temperature for a period of 14 months, and at 40°C/75% RH for a period of 6 months. The samples were analyzed to determine the amount of nebivolol, unknown impurities, and total impurities generated during the stability test.

The results of the stability study are shown in Table 3.

Table 3: Assay of nebivolol, percentage of total unknown impurities and total impurities after subjecting the ointment of Example 1 to different stability conditions

Composition	Stability condition	Assay (% w/w)	Impurity (% w/w)	
			Total unknown impurities	Total impurities
Example 1 (5.00%)	RT/14M	98.2	0.04	0.04
	40°C/75% RH/6M	96.4	0.04	0.04
Example 1 (10.00%)	RT/14M	98.1	0.03	0.03
	40°C/75% RH/6M	95.7	0.04	0.04
Example 1 (20.00%)	RT/14M	97.6	0.03	0.03
	40°C/75% RH/6M	97.0	0.04	0.04

The ointments of Example 1 were found to be stable under the subjected stability conditions.

Example 2

Ingredients	Quantity (% w/w)
Nebivolol hydrochloride equivalent to nebivolol	5.00
Propyl paraben	0.02
Methyl paraben	0.20
Propylene glycol	10.00
Hydroxyethyl cellulose	3.00
Polysorbate 80	0.50
Purified water	q.s. to 100.00

Manufacturing process:

- 5 1. Propyl paraben and methyl paraben were dissolved in heated purified water to obtain a solution.
2. Hydroxyethyl cellulose was dispersed into propylene glycol to obtain a dispersion.
3. The dispersion of step 2 was mixed with the solution of step 1 to obtain a mixture.
4. Nebivolol hydrochloride and polysorbate 80 were dispersed in heated purified water to
10 obtain a dispersion.
5. The mixture of step 3 was mixed with dispersion of step 4.
6. The mixture of step 5 was mixed with purified water to obtain a gel.
7. The gel of step 6 was packed into suitable sized tubes.

- 15 Similarly, compositions comprising nebivolol in strengths of 2.5% w/w, 10.00% w/w, and 20.00% w/w of the composition were also prepared according to the procedure described above. The pH of the compositions was found to be between 5.0 to 7.0 when subjected to stability conditions of 40°C/75% RH for a period of 1 month.

Example 3

Ingredients	Quantity (% w/w)
Nebivolol hydrochloride equivalent to nebivolol	5.00
Carbomer 980	2.50
Butylated hydroxy toluene	0.20
Polyethylene glycol 400	5.00
Propylene glycol	q.s. to 100.00

Manufacturing process:

1. Butylated hydroxy toluene was added to heated polyethylene glycol 400 to obtain a molten mixture.
2. Carbomer 980 was mixed with the molten mixture of step 1.
- 5 3. Nebivolol hydrochloride was dispersed into a part of propylene glycol to obtain a drug dispersion.
4. The drug dispersion of step 3 was mixed with the mixture of step 2.
5. The mixture of step 4 was mixed with the remaining part of propylene glycol to obtain a gel.
- 10 6. The gel of step 5 was packed into suitable sized tubes.

Similarly, compositions comprising nebivolol in strengths of 2.5% w/w, 10.00% w/w, and 20.00 % w/w of the composition were also prepared according to the procedure described above.

15 **Example 4**

Ingredients	Quantity (% w/w)
Nebivolol hydrochloride equivalent to nebivolol	2.50
Methyl paraben	0.14
Benzyl alcohol	1.00
Cetostearyl alcohol	6.00
Isopropyl myristate	5.00
Medium chain triglycerides	8.00
Polysorbate 80	3.00
Sorbitan monostearate	0.75
Butylated hydroxy toluene	0.02
Propylene glycol	5.00
Phosphoric acid	q.s.
Sodium phosphate	q.s.
Purified water	q.s. to 100.00

Manufacturing process:

1. Benzyl alcohol, cetostearyl alcohol, isopropyl myristate, medium chain triglycerides, polysorbate 80, sorbitan monostearate, and butylated hydroxy toluene were heated to obtain a molten mixture.

2. Propylene glycol and methyl paraben were dissolved in heated purified water to obtain a solution.
3. The solution of step 2 and the molten mixture of step 1 were mixed to obtain a mixture.
- 5 4. Nebivolol hydrochloride was dispersed into the mixture of step 3, and purified water was added to the mixture to obtain a gel.
5. Phosphoric acid and sodium phosphate were added to the gel of step 4 to adjust the pH to between 4.0 and 7.0.
6. The gel of step 5 was packed into suitable sized tubes.

10

Similarly, compositions comprising nebivolol in strengths of 5.00% w/w, 10.00% w/w, and 20.00% w/w of the composition were also prepared according to the procedure described above.

Stability Testing

- 15 The gels obtained from Examples 2, 3, and 4, after being packed in lami tubes, were subjected to stability testing at 40°C/75% RH for a period of 3 month. The samples were analyzed initially and after three months for determining the amount of nebivolol, unknown impurities, and total impurities generated during the stability test.

The results of the stability study are shown in Table 4.

20

Table 4: Assay of nebivolol, percentage of total unknown impurities and total impurities after subjecting gels of Examples 2, 3, and 4 to different stability conditions

Composition	Stability condition	Assay (% w/w)	Impurity (% w/w)	
			Total unknown impurities	Total impurities
Example 2 (2.5%)	Initial	102.10	0.02	0.02
	40°C/75% RH/3M	101.80	0.04	0.06
Example 2 (5.0%)	Initial	102.70	0.03	0.03
	40°C/75% RH/3M	101.70	0.03	0.06
Example 2 (10%)	Initial	104.70	0.03	0.03
	40°C/75% RH/3M	109.80	0.03	0.06

Example 2 (20%)	Initial	102.50	0.02	0.02
	40°C/75% RH/3M	101.20	0.03	0.05
Example 3 (2.5%)	Initial	97.90	0.04	0.04
	40°C/75% RH/3M	97.80	0.06	0.06
Example 3 (5%)	Initial	97.50	0.05	0.05
	40°C/75% RH/3M	97.60	0.04	0.04
Example 3 (10%)	Initial	95.60	0.04	0.04
	40°C/75% RH/3M	97.50	0.04	0.04
Example 3 (20%)	Initial	96.00	0.03	0.03
	40°C/75% RH/3M	101.40	0.03	0.03
Example 4 (2.5%)	Initial	95.90	0.02	0.03
	40°C/75% RH/3M	94.60	0.08	0.08
Example 4 (5%)	Initial	99.60	0.03	0.03
	40°C/75% RH/3M	99.20	0.06	0.06
Example 4 (10%)	Initial	99.10	0.02	0.02
	40°C/75% RH/3M	98.10	0.05	0.05
Example 4 (20%)	Initial	99.70	0.04	0.04
	40°C/75% RH/3M	98.60	0.04	0.04

The gels of Examples 2, 3, and 4 were found to be stable under the subjected stability conditions.

Example 5

Ingredients	Quantity (% w/w)
Nebivolol hydrochloride equivalent to nebivolol	0.50
Methyl paraben	0.20
Benzyl alcohol	1.0
Propylene glycol	15.0
Hydroxyethyl cellulose	1.75
Purified water	q.s. to 100.00

Manufacturing process:

- 5 1. Methyl paraben was dissolved in heated purified water to obtain a solution.
2. Hydroxyethyl cellulose was dispersed into a part of propylene glycol to obtain a dispersion.
3. Nebivolol hydrochloride and benzyl alcohol were dispersed into the remaining part of propylene glycol to obtain a drug dispersion.
- 10 4. The dispersion of step 2 was mixed with the dispersion of step 3 to obtain a mixture.
5. The mixture of step 4 was mixed with purified water to obtain a gel.
6. The gel of step 5 was packed into suitable sized tubes.

Similarly, compositions comprising nebivolol in strengths of 1.50% w/w, 3.00% w/w, and 4.50% w/w of the composition were also prepared according to the procedure described above. The pH of the compositions were found to be between 3.0 to 4.0.

Example 6

Ingredients	Quantity (% w/w)
Nebivolol hydrochloride equivalent to nebivolol	0.50
Carbomer 980	2.50
Propylene glycol	q.s. to 100.00

5 **Manufacturing process:**

1. Carbomer 980 was added to a part of propylene glycol to obtain a mixture.
2. Nebivolol hydrochloride was dispersed in the remaining part of propylene glycol to obtain a dispersion.
3. The dispersion of step 2 was mixed with mixture of step 1 to obtain a gel.
- 10 4. The gel of step 3 was packed into suitable sized tubes.

Similarly, compositions comprising nebivolol in strengths of 1.50% w/w, 3.00% w/w, and 4.50% w/w of the composition were also prepared according to the procedure described above.

Example 7

Ingredients	Quantity (% w/w)
Nebivolol hydrochloride equivalent to nebivolol	0.50
Methyl paraben	0.20
Benzyl alcohol	1.00
Cetostearyl alcohol	6.00
Isopropyl myristate	5.00
Polysorbate 60	3.00
Sorbitan monostearate	0.75
Propylene glycol	10.00
Phosphoric acid	q.s.
Sodium phosphate	q.s.
Purified water	q.s. to 100.00

15 **Manufacturing process:**

1. Cetostearyl alcohol, isopropyl myristate, polysorbate 60, and sorbitan monostearate were heated to obtain a molten mixture.
2. Methyl paraben was dissolved in heated purified water to obtain a solution.

3. The solution of step 2 and the molten mixture of step 1 were mixed to obtain a mixture.
4. Nebivolol hydrochloride and benzyl alcohol were dispersed into propylene glycol to obtain a dispersion.
- 5 5. The dispersion of step 4 was mixed with the mixture of step 3.
6. The mixture of step 5 was mixed with purified water to obtain a gel.
7. Phosphoric acid and sodium phosphate were added to the gel of step 6 to adjust the pH to between 4.0 and 7.0.
8. The gel of step 7 was packed into suitable sized tubes.

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Similarly, compositions comprising nebivolol in strengths of 1.50% w/w, 3.00% w/w, and 4.50% w/w of the composition were also prepared according to the procedure described above.

We claim:

- 1 1. A stable topical pharmaceutical composition of nebivolol for the treatment of diabetic
2 wounds in a subject, wherein the time for complete wound closure (in days) after
3 topical administration of the composition is less than or equal to that of becaplermin
4 gel.
- 1 2. The stable topical pharmaceutical composition of nebivolol according to claim 1,
2 wherein the nebivolol is nebivolol hydrochloride.
- 1 3. The stable topical pharmaceutical composition of nebivolol according to claim 1,
2 wherein the pharmaceutical composition provides 100% re-epithelialization of the
3 wound.
- 1 4. The stable topical pharmaceutical composition of nebivolol according to claim 1,
2 wherein the composition is in the form of a cream, gel, powder, lotion, ointment,
3 liniment, solution, suspension, paste, aerosol, or spray.
- 1 5. The stable topical pharmaceutical composition of nebivolol according to claim 4,
2 wherein the ointment is a paraffin-based ointment.
- 1 6. The stable topical pharmaceutical composition of nebivolol according to claim 1,
2 wherein the topical composition is applied topically once, twice, or thrice daily for one
3 to three weeks.
- 1 7. The stable topical pharmaceutical composition of nebivolol according to claim 1,
2 wherein the pharmaceutical composition further comprises pharmaceutically
3 acceptable excipients selected from the group comprising viscosity enhancers,
4 emollients, surfactants, preservatives, chelating agents, anti-oxidants, pH-adjusting
5 agents, solvents, co-solvents, vehicles, and mixtures thereof.
- 1 8. The stable topical pharmaceutical composition of nebivolol according to claim 1,
2 wherein the pharmaceutical composition is prepared by a process comprising:
 - 3 (i) dispersing nebivolol in a solvent to obtain a drug dispersion;
 - 4 (ii) mixing pharmaceutically acceptable excipients with the drug dispersion of
5 step i) to obtain a mixture;
 - 6 (iii) optionally, melting the mixture of step ii) to obtain a molten mixture;

- 7 (iv) mixing the mixture of ii) or the molten mixture of step iii) with a vehicle to
8 obtain the desired composition; and
9 (v) filling the composition of step iv) into a suitable sized container.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB15/59742

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61K 31/352; A61P 3/10 (2015.01) CPC - A61K 31/00, 31/352 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(8): A61K 31/352; A61P 3/10 (2015.01) CPC: A61K 31/00, 31/352 USPC: 514/456 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) PATSEER (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, Other Countries (INPADOC), RU, AT, CH, TH, BR, PH); EBSCO; Google Scholar; IP.com; KEYWORDS: nebivolol, nebilet, bystolic, nebivolol hydrochloride, topical administ*, cream*, ointment*, diabetic wound*, wound* closure, epithelialization, PDGF BB, becaplermin, diabetic ulcer*, ulcer* healing, adren* antagonist*, beta blocker*		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2011/0021526 A1 (DESHPANDE, SK) 27 January 2011; paragraphs [0017], [0047], [0080]	1-8
A	EMBIL, JM et al., Recombinant human platelet-derived growth factor-BB (becaplermin) for healing chronic lower extremity diabetic ulcers: an open-label clinical evaluation of efficacy, Wound Repair and Regeneration 8(3), pages 162-168, 2000; abstract; page 185, column 1, paragraph 3	1-8
A	US 2014/0314711 A1 (GENENTECH, INC.) 23 October 2014; paragraphs [0032], [0035], [0409]; claim 125	1-8
A	US 2012/0329729 A1 (RODGERS, KE et al.) 27 December 2012; paragraphs [0004]-[0005], [0099]	1-8
☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.		
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Date of the actual completion of the international search 16 March 2016 (16.03.2016)		Date of mailing of the international search report 07 APR 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300		Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774