

Method of Enhancing the Systemic Hypoglycemic Effect of Topically Applied Insulin with the Use of Prostaglandin Analogues: A Novel Fixed Combination Eye Drop Formulation of Insulin and Prostaglandin Analogue for the Lowering of Blood Glucose Level

Specification

Technical Field of the Invention

This invention relates to a method of increasing the systemic hypoglycemic effect of insulin when applied topically to the eye through the use of prostaglandin analogues as penetration enhancers, more specifically, to an ophthalmic composition of insulin and prostaglandin analogue for the lowering of blood glucose level.

Background of the Invention

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia or elevated blood sugar levels, affecting millions of individuals worldwide (International Diabetes Federation, 2019).

According to the International Diabetes Federation (IDF), as of 2021, an estimated 537 million adults worldwide are living with diabetes, which represents approximately one in eleven adults. Due to factors such as aging populations, urbanization, and lifestyle changes, including unhealthy diets and reduced physical activity, the prevalence of diabetes is increasing globally. Diabetes is a significant cause of morbidity and mortality, with complications such as cardiovascular disease, kidney disease, nerve damage, and blindness. The IDF estimates that diabetes was responsible for 4.2 million deaths in 2019, making it one of the leading causes of death worldwide.

Insulin therapy is the cornerstone of treatment for type 1 diabetes and often required for advanced type 2 diabetes.

Insulin is a hormone used to lower blood glucose to normal levels. It achieves its hypoglycemic effect by promoting the uptake and storage of glucose in the body's tissues. There are several types of insulin products available, which can be classified based on their onset, peak, and duration of action. These differences in action profiles allow healthcare providers to tailor insulin therapy to the individual needs of patients with diabetes. The main types of insulin include:

Rapid-acting insulin:

Rapid-acting insulins start working within 15 minutes of administration, peak at approximately 1 hour, and last for 2-4 hours. They are typically taken just before or with meals to help control post-meal blood sugar spikes. Examples include insulin lispro (Humalog), insulin aspart (NovoLog), and insulin glulisine (Apidra).

1 Short-acting insulin:

2 Also known as regular or soluble insulin, short-acting insulin begins to work within 30
3 minutes to an hour, peaks at 2-4 hours, and lasts for 5-8 hours. It is usually taken 30
4 minutes before meals. Examples include Humulin R and Novolin R.

5

6 Intermediate-acting insulin:

7 Intermediate-acting insulins have a slower onset and longer duration of action
8 compared to short-acting insulin. They start working within 1-2 hours, peak at 4-12
9 hours, and last for 12- 18 hours. They are typically used to provide basal insulin
10 coverage throughout the day.

11

12 Examples include NPH insulin (Neutral Protamine Hagedorn), such as Humulin N
13 and Novolin N.

14

15 Long-acting insulin:

16 Long-acting insulins provide a slow, steady release of insulin with no pronounced
17 peak, lasting for 15 up to 24 hours or longer. They are used to provide basal insulin
18 coverage and are often combined with rapid- or short-acting insulin to cover mealtime
19 blood sugar spikes. Examples include insulin glargine (Lantus, Toujeo), insulin detemir
20 (Levemir), and insulin degludec (Tresiba).

21

22 The chemical properties of different insulin types, including their amino acid
23 sequences and molecular structures, play a crucial role in determining their rate of
24 absorption.

25 Insulin molecules exist as monomers or can aggregate into dimers or hexamers.
26 These aggregation states influence the rate of insulin absorption. Insulin monomers
27 are more soluble and are absorbed more rapidly than dimers or hexamers.

28

29 Below is an overview of the chemical properties of various insulin types and how they
30 affect the rate of absorption:

31 Rapid-acting insulin analogs:

32 Rapid-acting insulins are engineered to have minor alterations in their amino acid
33 sequences compared to human insulin. These changes result in altered insulin
34 molecules that do not self-aggregate into hexamers as readily as regular insulin,
35 promoting faster absorption into the bloodstream.

36

37 For example:

38 Insulin lispro (Humalog) has a reversal of proline and lysine at positions B28 and B29.
39 This change disrupts the hexamer formation and enhances its solubility, leading to
40 faster absorption.

41

42 Insulin aspart (NovoLog) has a proline at position B28 replaced with an aspartic acid,
43 which also reduces hexamer formation and increases the rate of absorption.

44

1 Insulin glulisine (Apidra) has asparagine at position B3 replaced with a lysine and a
2 lysine at position B29 replaced with a glutamic acid, which results in faster dissociation
3 into monomers and quicker absorption.

4
5 Short-acting insulin (Regular insulin):

6 Regular insulin, which is structurally identical to human insulin, forms hexamers in the
7 presence of zinc ions. These hexamers must dissociate into dimers and then
8 monomers before they can be absorbed into the bloodstream. This dissociation
9 process slows down the absorption of regular insulin compared to rapid-acting
10 analogs.

11
12 Intermediate-acting insulin (NPH):

13 NPH insulin is a suspension of human insulin combined with protamine, a protein that
14 forms a complex with insulin. The protamine-insulin complex has reduced solubility,
15 which slows down the absorption of insulin from the injection site into the
16 bloodstream, resulting in an intermediate duration of action.

17
18 Long-acting insulin analogs:

19 Long-acting insulin analogs have modifications in their amino acid sequences or
20 additional components that slow down their absorption and prolong their action.

21
22 For example:

23 Insulin glargine (Lantus, Toujeo) has a glycine substituted for asparagine at position
24 A21 and two arginines added to the B-chain. These changes make insulin glargine
25 less soluble at physiological pH, causing it to precipitate at the injection site. The
26 precipitate slowly dissolves over time, providing a slow, steady release of insulin.

27
28 Insulin detemir (Levemir) has a myristic acid fatty acid chain attached to lysine at
29 position B29. This modification increases the binding of insulin detemir to albumin in
30 the bloodstream and at the injection site, slowing down its absorption and prolonging
31 its duration of action.

32
33 Insulin degludec (Tresiba) has a hexadecanedioic acid side chain at position B29,
34 which facilitates the formation of multi-hexamers. These multi-hexamers slowly
35 release monomers, resulting in a prolonged and stable action profile.

36
37 Insulin is primarily administered by subcutaneous injections. The delivery of insulin via
38 the ocular route has been challenging because of ocular barriers. These ocular
39 barriers, while essential for the eye's protection and homeostasis, present significant
40 challenges for delivering insulin via eye drops. Overcoming these barriers is crucial for
41 the development of a viable ocular insulin delivery system.

42
43 Insulin is a large molecule that consists of 51 amino acids. It has a molecular weight
44 of approximately 5.8 kD. Its relatively large size results in poor passive diffusion
45 across the ocular barriers — the corneal epithelium, tight junctions between cells,
46 active efflux transporters — significantly reducing its absorption and bioavailability
47 when delivered via eye drops.

1
2 In addition, the lipophilic nature of the corneal epithelium poses a considerable barrier
3 to the absorption of hydrophilic molecules. Insulin exhibits hydrophilic properties,
4 which further impedes its passive diffusion.

5
6 In addition to the corneal barrier, the conjunctiva and sclera contribute to ocular drug
7 absorption limitations. While these tissues are more permeable to hydrophilic
8 molecules than the cornea, their ability to permit the passage of large molecules like
9 insulin is still limited.

10
11 Ocular absorption is also affected by precorneal factors. Eye drops have a short
12 residence time due to rapid evacuation through tear drainage. Further, tear fluid
13 contains peptidases and proteases that can potentially degrade insulin, reducing its
14 bioavailability.

15
16 Currently, there are no insulin eye drops available to lower blood glucose levels.
17 Insulin is typically administered through injections or an insulin pump, as it needs to
18 be delivered directly into the bloodstream to be effective.

19
20 The present invention leverages a previously undescribed effect of prostaglandin and
21 prostaglandin analogues on the permeability of the cornea and conjunctiva to large
22 molecules for use as a penetration enhancer for insulin.

23
24 Prostaglandin and prostaglandin analogues have been used clinically as ocular
25 hypotensives since 1998. The first prostaglandin analogue to be approved by the
26 FDA for clinical ophthalmic use is Latanoprost. Later drugs include Unoprostone,
27 Travoprost, Bimatoprost, Tafluprost, Latanoprostene.

28
29 Prostaglandin analogues are prodrugs which are hydrolyzed in the cornea into their
30 active form to selectively stimulate the prostaglandin F₂ alpha receptor to cause up-
31 regulation of matrix metalloproteinases and remodeling of the extracellular matrix in
32 the structures of the eye adjacent to Schlemm's canal where aqueous humor drains.
33 These actions result in higher tissue permeability of these structures, thereby
34 decreasing outflow resistance to aqueous which results in a drop in intraocular
35 pressure. Aqueous contains cells and large proteins

36
37 Although no studies have been performed to show similar effects on the cornea,
38 changes in biomechanical properties of the cornea after local prostaglandin analogue
39 treatment suggest that similar changes occur in the cornea.

40
41 The application of latanoprost has been shown to increase corneal hysteresis not
42 correlated with the drug-induced decrease in the intraocular pressure. This suggests
43 a direct effect of latanoprost on the viscoelastic corneal properties^{[1], [2], [3]}.

44
45 Other prostaglandin analogues (travoprost, latanoprost and bimatoprost) have
46 likewise been associated with different extents of reduction in tissue stiffness and
47 changes in corneal microstructure^[4].

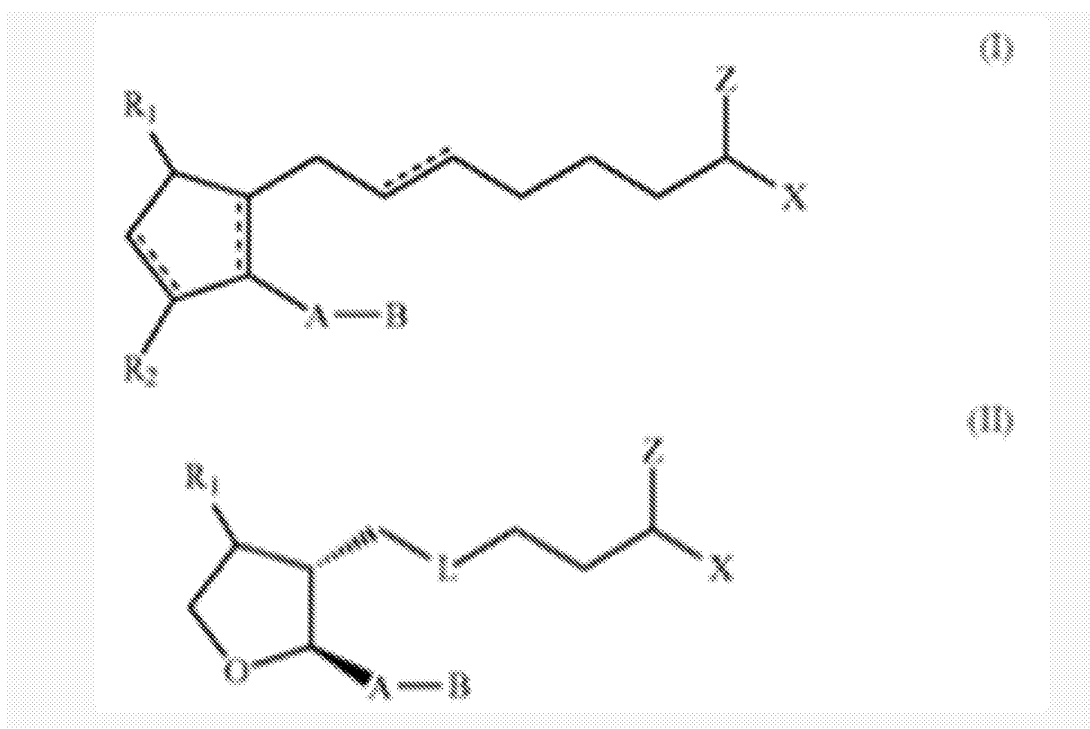
48
49 The biomechanical effects of prostaglandin analogues on the cornea suggest that
50 changes to corneal tissue permeability may also be occurring, although no studies

1 have been performed to confirm this. The present invention leverages this effect to
2 increase the ocular absorption of topical insulin.

3
4 **Prior Art**

5
6 U.S. Patent No. 10,335,418 ('418):

7
8 The '418 patent discloses a method and composition for treating metabolic
9 syndrome, or a disorder associated with metabolic syndrome, e.g. obesity,
10 dyslipidemia, and/or a diabetic condition. An F-series prostaglandin (i.e., latanoprost)
11 according to the following formulas (I) and (II) are used:
12



13
14
15 These include a compound of Formulas (I) or (II), or a pharmaceutically acceptable
16 salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched
17 derivative, or prodrug thereof. The compounds are administered by any contemplated
18 systemic route. A pharmaceutical composition of the formulas can be prepared,
19 packaged, and/or sold in a formulation suitable for ophthalmic administration. Such
20 formulations may, for example, be in the form of eye drops.

21
22 This reference fails to teach insulin-latanoprost preparation. For '418, there is no
23 insulin involved. It is a patent purely on prostaglandin and not insulin.

International (WIPO) Patent Publication No. WO2010097800 ('800):

The '800 reference teaches a non-hypoglycemic or euglycemic combination of insulin and prostaglandin analogues through invasive methods such as injecting, implanting and/or inserting in/ or adjacent to the Schlemm's canal or at other ocular tissues and sites related to or surrounding the Schlemm's canal for the purpose of lowering intraocular pressure.

This reference fails to teach the use of prostaglandin analogues as a penetration enhancer to enhance ocular absorption of topically applied insulin. It also fails to teach a combination of insulin and prostaglandin analogues for topical ocular application to lower blood glucose levels. The disclosure specifically excludes hypoglycemic compositions by specifically limiting itself to euglycemic insulin.

Summary and Objective of the Invention

The primary objective of this invention is to :

Provide a method to increase the penetration of insulin when applied topically to the eye;

Utilize the penetration-enhancing properties of the prostaglandin analogues to facilitate the transport of insulin across the corneal and conjunctival barriers, resulting in improved bioavailability and therapeutic efficacy;

Provide a formulation comprising an insulin and a prostaglandin analogue that causes a significant systemic hypoglycemic effect in order to manage diabetes mellitus;

Provide a comfortable and patient-friendly alternative to subcutaneous insulin injections, reducing the burden of frequent injections and improving patient compliance; and

Offer a versatile platform for ocular drug delivery, which can be further tailored and optimized for the administration of other therapeutic agents with limited ocular penetration.

The present invention is directed to a novel insulin delivery system that utilizes the ocular application of the insulin.

The present invention is directed to a novel insulin delivery system that provides at least an insulin, in a form of rapid- or short-acting type, and at least a prostaglandin analogue.

The present invention is directed to a novel insulin formulation that comprises at least an insulin, in a form of rapid- or short-acting type, and at least a prostaglandin analogue.

The present invention is directed to an insulin with a prostaglandin analogue formulation further comprising excipients used in ocular application.

1
2 The present invention is directed to a process of manufacturing an ocular application
3 solution with insulin and prostaglandin analogue.
4

5 This invention has the potential to revolutionize the management of diabetes mellitus
6 by offering a convenient method of insulin administration while avoiding the
7 complications and challenges associated with traditional subcutaneous injections.
8

9 **Detailed Description of the Invention**

10
11 The present invention will be further disclosed in the following paragraphs.
12

13 The terminologies used in the disclosure will be considered as used in the field of
14 technology of the present invention. No new usage of these words are being
15 introduced into the further disclosure.
16

17 As already presented in the previous sections, the present invention is directed to a
18 novel ocular insulin delivery system that utilizes prostaglandin analogue as penetration
19 enhancer.
20

21 The present invention utilizes insulin identified as rapid-acting or short-acting insulin.
22

23 The present invention utilizes rapid-acting insulin such as but not limited to: Insulin
24 lispro, and Insulin aspart.
25

26 The present invention utilizes short-acting insulin such as but not limited to Regular
27 insulin (insulin R).
28

29 The present invention utilizes prostaglandin analogues as penetration enhancers.
30

31 The present invention utilizes prostaglandin analogues such as, but not limited to, the
32 following: latanoprost, bimatoprost, travoprost, or tafluprost.
33

34 The present invention leverages the corneal penetration-enhancing properties of
35 prostaglandin analogues to facilitate the transport of insulin across the corneal and
36 conjunctival barriers, resulting in a significant systemic hypoglycemic effect.
37

38 The present invention utilizes the excipients and other ingredients which are
39 commonly used in the preparation of an ocular medication such as, but not limited to:
40

41 Preservatives: benzalkonium chloride (final concentration range can be from 0.005%
42 to 0.08%);
43

44 Surfactants: polysorbate 80, polyoxyl 40 hydrogenated castor oil, metacresol;
45

46 Chelating agents: disodium edetate, tromethamine;
47

48 Buffering agents: sodium phosphate dibasic, sodium phosphate monobasic, citric
49 acid monohydrate, sodium hydrogen phosphate dihydrate, hydrochloric acid, sodium
50 hydroxide, boric acid, sodium borate;

1 Viscosity enhancers: HPMC 4000 cps, PVA, Carbomer, PEG, Na hyaluronate,
2 glycerin;

3
4 Tonicity agents: sodium chloride, glycerol, zinc chloride, zinc oxide pH adjusting
5 agents: HCl / NaOH q.s. to pH 6.4 to 7.4; and

6
7 Solvent: water for injection.

8
9 The concentration of insulin in the present invention ranges from 1.735 mg/mL to 69.4
10 mg/mL or a percentage of 0.1735% to 6.94%.

11
12 The concentration of prostaglandin analogue in the present invention ranges are
13 different depending on which analogue will be used.

14
15 For Latanaprost, the final concentration range is from 0.000625% to 0.2%.

16
17 For Unoprostone, the final concentration range is from 0.015% to 0.6%.

18
19 For Travoprost, the final concentration range can be from 0.002% to 0.16%.

20
21 For Bimatoprost, the final concentration range can be from 0.00125% to 0.12%.

22 For Tafluprost, the final concentration range can be from 0.00018775% to 0.06%.

23
24 Prostaglandin analogues are relatively insoluble and must be dissolved together with
25 a surfactant at a high temperature typically at 80 degrees C then cooled down before
26 mixing with insulin because insulin denatures above 40 degrees celsius.

27
28 Insulin itself is relatively insoluble at pH 6.4 to 7.4 and must be dissolved in water at
29 pH 2 - 3. The pH is then adjusted through buffering until the desired pH of 6.4 to 7.4
30 is achieved.

31
32 The present invention is prepared by mixing a solution of the selected insulin in water
33 at the appropriate concentration with its pH adjusted to 6.4 to 7.4, with a solution of
34 the selected prostaglandin analogue, likewise dissolved in water together with the
35 selected surfactant at the appropriate concentration with its pH similarly adjusted. The
36 selected excipients are added to the combination while maintaining the pH through
37 buffering. The mixture is gently agitated until the components are thoroughly
38 combined, resulting in a homogeneous insulin eye drop solution.

39
40 The present invention is administered topically onto the eye depending on the amount
41 as recommended by the user's health care professional.

42
43 As established in the background of the present invention, there are different factors
44 that hinder the application of insulin via the ocular route. The most prominent factors
45 are the biological factors and how insulin interacts with these.

46
47 As a relatively large molecule, insulin poses a significant challenge for ocular
48 absorption. Insulin also has 18 hydrophilic residues on its surface which renders it
49 difficult to be absorbed through the lipophilic barriers of the eye. Tear turnover

1 through the nasolacrimal drainage also reduces drug contact time with the cornea
2 thus limiting absorption.

3
4 The technical solution being presented by the invention which was not disclosed by
5 the prior art is the use of prostaglandin analogues as penetration enhancers for insulin
6 and the combination of prostaglandin analogue with insulin for lowering blood glucose
7 level. It was not known previously that this combination of drugs is possible for lowering
8 blood glucose level through topical ocular application.

9
10 As found in prior art, prostaglandin analogues are hydrolyzed in the cornea into their
11 active form to selectively stimulate the prostaglandin F2 alpha receptor to cause up-
12 regulation of matrix metalloproteinases and remodeling of the extracellular matrix in
13 the structures of the eye adjacent to Schlemm's canal where aqueous humor drains.
14 These actions result in higher tissue permeability of these structures, thereby
15 decreasing outflow resistance to aqueous which results in a drop in intraocular
16 pressure.

17
18 This mechanism also allows the increased uptake of insulin that is applied topically
19 onto the eye, thus resolving the problems of the prior arts.

20
21 To further increase the uptake of insulin, excipients such as polysorbate 80 and
22 benzalkonium chloride are being used by the present invention. These excipients
23 affect the corneal epithelial barrier to allow increased paracellular transport.

24
25 This novel administration of the insulin formulation also allows increased compliance
26 by users since it removes the fear of needles which is a very invasive method of
27 introducing insulin into the bloodstream.

28 The present invention is further discussed in the following specific examples which are
29 not aimed to limit the scope but instead gives embodiments on which the present
30 invention was used and tested.

31 32 **Examples**

33
34 Example 1. Formulation of Insulin Eye Drop using Insulin regular and Latanoprost

35		
36	Insulin regular	0.1735%
37	Latanoprost	0.0025%
38	Benzalkonium Chloride	0.01%
39	Polysorbate 80	0.1%
40	Buffering agent	q.s buffer capacity nmt 0.5%
41	Tonicity agent	0.5-2% NaCl *quantity sufficient to osmolality
42		approx. 308 mOsMol/Kg*
43	Solvent	q.s. 2.5 mL
44		
45		

Example 2. Formulation of Insulin Eye Drop using Insulin lispro and Tafluprost

Insulin lispro	0.1735%
Tafluprost	0.0025%
Polysorbate 80	0.5%
Buffering agent	q.s buffer capacity nmt 0.5%
Tonicity agent	0.5-2% NaCl *quantity sufficient to osmolality approx. 308 mOsMol/Kg*
Solvent	q.s. 2.5 mL

Example 3. Formulation of Insulin Eye Drop using Insulin aspart and Bimatoprost

Insulin aspart	6.94%
Bimatoprost	0.12%
Benzalkonium Chloride	0.01%
Polysorbate 80	0.5%
Buffering agent	q.s buffer capacity nmt 0.5%
Tonicity agent	0.5-2% NaCl *quantity sufficient to osmolality approx. 308 mOsMol/Kg*
Solvent	q.s. 2.5 mL

Example 4. Formulation of Insulin Eye Drop using Insulin regular and Travoprost

Insulin regular	0.1735%
Travoprost	0.002%
Polysorbate 80	0.5%
Buffering agent	q.s buffer capacity nmt 0.5%
Tonicity agent	0.5-2% NaCl *quantity sufficient to osmolality approx. 308 mOsMol/Kg*
Solvent	q.s. 2.5 mL

Example 5. Formulation of Insulin Eye Drop using Insulin regular and Unoprostone

Insulin regular	0.1735%
Unoprostone	0.015%
Benzalkonium chloride	0.01%
Polysorbate 80	0.5%
Buffering agent	q.s buffer capacity nmt 0.5%
Tonicity agent	0.5-2% NaCl *quantity sufficient to osmolality approx. 308 mOsMol/Kg*
Solvent	q.s. 2.5 mL

Example 6. Insulin regular with Latanoprost dose response

Fasting interstitial glucose was measured (using an Abbott Freestyle Libre Continuous Glucose Monitor). The test drug (0.1735% insulin r vs 0.1735 insulin r + 0.0025% latanoprost) was instilled in both eyes thereafter. Interstitial glucose was then measured serially for 8 hours. Fasting levels - trough levels and time to trough in hours were compared relative to the fasting levels.

1

	0.02 mL insulin r only	0.02 mL insulin r + latanoprost @ eye	0.02 mL insulin r + latanoprost @ eye	0.05 mL insulin r + latanoprost @ eye	0.10 mL insulin r + latanoprost @ eye
Fasting mg/dL	159	144	132	146	141
Trough mg/dL	152	115	100	100	67
Fasting - trough mg/dL	7	29	32	46	74
Time to trough hrs.	n/a	5	2	6.5	5

2

3 Example 7. Insulin lispro with Tafluprost (no BAK)

4

5 Fasting interstitial glucose was measured (using an Abbott Freestyle Libre Continuous
6 Glucose Monitor). The test drug (.1735% insulin lispro vs .1735% insulin lispro +
7 .0025% latanoprost) was instilled in both eyes thereafter. Interstitial glucose was then
8 measured serially for 3 hours. Levels at 3 hours were compared relative to the fasting
9 levels.

10

	0.02 mL lispro @eye	0.02 mL lispro + tafluprost @eye	0.05 mL lispro + tafluprost @eye
Fasting mg/dL	112	162	144
3 hours mg/dL	108	129	91
Difference	4	33	53

11

12 ^[1] G Bolivar, et al. Effect of topical prostaglandin analogues on corneal
13 hysteresis. Acta Ophth. 29 February 2015. Volume 93, Issue 6. P. e495
14 toe4985

15 ^[2] N Wu, et al. Changes in Corneal Biomechanical Properties after Long-Term
16 Topical Prostaglandin Therapy. PLOS ONE. 17 May 2016.

17 ^[3] P Tsikripis, et al. The effect of prostaglandin analogs on the biomechanical
18 properties and central thickness of the cornea of patients with open-angle
19 glaucoma: a 3-year study on 108 eyes. Drug Design, Development and
20 Therapy. 3 October 2022. Volume 7, 2013 pages 1149- 1156

21 ^[4] J Wang, et al. Effect of travoprost, latanoprost and bimatoprost PGF2 α
22 treatments on the biomechanical properties of in-vivo rabbit cornea. Exp Eye
23 Res. Volume 215 February 2022, 108920

Claims

1. A pharmaceutical composition for the treatment of diabetes mellitus via ocular application, comprising: an insulin; a set of excipients; and a penetration enhancer, wherein the penetration enhancer is a prostaglandin analogue.
2. The pharmaceutical composition for the treatment of diabetes mellitus via ocular application according to claim 1, wherein the insulin is selected from rapid-acting or short- acting insulin.
3. The pharmaceutical composition for the treatment of diabetes mellitus via ocular application according to claim 2, wherein the rapid-acting insulin is selected from Insulin lispro and Insulin aspart.
4. The pharmaceutical composition for the treatment of diabetes mellitus via ocular application according to claim 2, wherein the short-acting insulin is Regular insulin (insulin R).
5. The pharmaceutical composition for the treatment of diabetes mellitus via ocular application according to claim 1, wherein the prostaglandin analogue is selected from latanoprost, unoprostone, bimatoprost, travoprost, tafluprost and latanoprostene.
6. The pharmaceutical composition for the treatment of diabetes mellitus via ocular application according to claim 1, wherein the set of excipients are further comprising:
 - a surfactant;
 - a buffering agent;
 - a viscosity enhancer;
 - a tonicity agent;
 - a preservative; and
 - a solvent.
7. The pharmaceutical composition for the treatment of diabetes mellitus via ocular application according to claim 6, wherein the surfactant is selected from polysorbate 80, polyoxyl 40 hydrogenated castor oil, and metacresol.
8. The pharmaceutical composition for the treatment of diabetes mellitus via ocular application according to claim 6, wherein the buffering agent is selected from sodium phosphate dibasic, sodium phosphate monobasic, citric acid monohydrate, boric acid, sodium hydrogen phosphate dihydrate, hydrochloric acid, sodium hydroxide, sodium citrate dihydrate, and sodium borate.
9. The pharmaceutical composition for the treatment of diabetes mellitus via ocular application according to claim 6, wherein the viscosity enhancers is selected from hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose (HEC), or carboxymethyl cellulose (CMC), and sodium hyaluronate.

- 1 10. The pharmaceutical composition for the treatment of diabetes mellitus via
2 ocular application according to claim 6, wherein the tonicity agent is selected
3 from sodium chloride, glycerol, zinc chloride, and zinc oxide.
4
- 5 11. The pharmaceutical composition for the treatment of diabetes mellitus via
6 ocular application according to claim 6, wherein the preservative is selected
7 from benzalkonium chloride, phenol, and sorbic acid.
8
- 9 12. The pharmaceutical composition for the treatment of diabetes mellitus via
10 ocular application according to claim 6, wherein the solvent is water.
11
- 12 13. The pharmaceutical composition for the treatment of diabetes mellitus via
13 ocular application according to claim 6, wherein the set of excipients may
14 further comprise a chelating agent.
15
- 16 14. The pharmaceutical composition for the treatment of diabetes mellitus via
17 ocular application according to claim 13, wherein the chelating agent is selected
18 from disodium edetate, and tromethamine.
19
- 20 15. The pharmaceutical composition for the treatment of diabetes mellitus via
21 ocular application according to claims 1 and 2, wherein the concentration of the
22 insulin ranges from 1.735 mg/mL to 34.7 mg/mL.
23
- 24 16. The pharmaceutical composition for the treatment of diabetes mellitus via
25 ocular application according to claims 1 and 3, wherein the concentration of
26 latanoprost ranges from 0.000625% to 0.2%.
27
- 28 17. The pharmaceutical composition for the treatment of diabetes mellitus via
29 ocular application according to claims 1 and 3, wherein the concentration of
30 unoprostone ranges from .015% to .6%
31
- 32 18. The pharmaceutical composition for the treatment of diabetes mellitus via
33 ocular application according to claims 1 and 3, wherein the concentration of
34 travoprost ranges from 0.002% to 0.16%
35
- 36 19. The pharmaceutical composition for the treatment of diabetes mellitus via
37 ocular application according to claims 1 and 3, wherein the concentration of
38 bimatoprost ranges from 0.00125% to 0.12%.
39
- 40 20. The pharmaceutical composition for the treatment of diabetes mellitus via
41 ocular application according to claims 1 and 3, wherein the concentration of
42 tafluprost ranges from 0.0001875% to 0.06%.
43
- 44 21. A method of lowering blood glucose level, comprising the step of administering
45 an effective amount of insulin and penetration enhancer to an eye.
46
- 47 22. The method of lowering blood glucose level according to claim 21, wherein said
48 insulin is selected from rapid-acting or short-acting insulin.
49

- 1 23. The method of lowering blood glucose level according to claim 21, wherein said
2 rapid- acting insulin is selected from Insulin lispro and Insulin aspart.
3
- 4 24. The method of lowering blood glucose level according to claim 21, wherein said
5 short-acting insulin is Regular insulin (insulin R).
6
- 7 25. The method of lowering blood glucose level according to claim 21, wherein said
8 insulin is selected from Insulin lispro, Insulin aspart, and Regular insulin (insulin
9 R).
10
- 11 26. The method of lowering blood glucose level according to claim 21, wherein said
12 penetration enhancer is a prostaglandin analogue.
13
- 14 27. The method of lowering blood glucose level according to claims 21 and 25,
15 wherein said penetration enhancer is selected from latanoprost, unoprostone,
16 bimatoprost, travoprost, tafluprost and latanoprostene.
17
- 18 28. Method of increasing the absorption of insulin when applied topically to the eye
19 by using prostaglandin analogues as penetration enhancers.
20
- 21 29. Method of increasing the absorption of insulin when applied topically to the eye
22 according to claim 28 wherein said insulin is selected from Insulin lispro, Insulin
23 aspart, and Regular insulin (insulin R).
24
- 25 30. Method of increasing the absorption of insulin when applied topically to the eye
26 according to claim 28 wherein said prostaglandin analogue is selected from
27 latanoprost, unoprostone, bimatoprost, travoprost, tafluprost and
28 latanoprostene.