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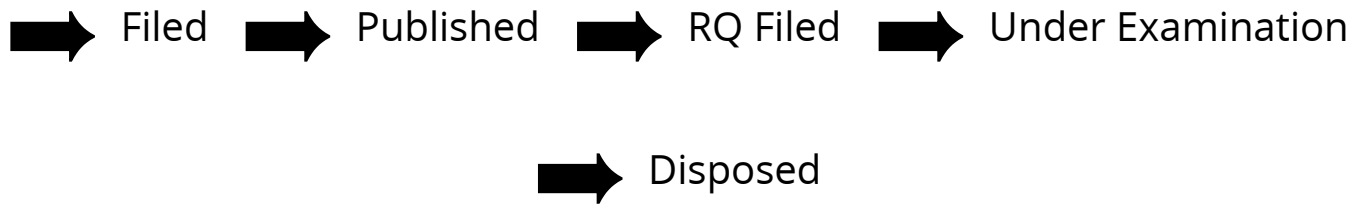


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APPLICANT NAME	1 . TULSHI CHAKRABORTY 2 . SUMEET GUPTA 3 . VIPIN SAINI
TITLE OF INVENTION	A PHARMACEUTICAL TOPICAL COMPOSITION AND METHOD OF PREPARATION FOR TREATING DERMATOLOGICAL MANIFESTATION OF DIABETES MELLITUS
FIELD OF INVENTION	CHEMICAL
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FORM 2
THE PATENTS ACT 1970
(39 of 1970)
&
THE PATENT RULES, 2003
COMPLETE SPECIFICATION
(See section 10 and rule 13)

1. TITLE OF THE INVENTION: - A PHARMACEUTICAL TOPICAL COMPOSITION AND METHOD OF PREPARATION FOR TREATING DERMATOLOGICAL MANIFESTATION OF DIABETES MELLITUS THERE OF

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3. PREAMBLE OF THE DESCRIPTION

The following specification particularly describes the invention and the manner in which it is to be performed

FIELD OF THE INVENTION

The present invention relates to the field of Pharmaceutical preparation technology and method of preparation relates topical composition for treating dermatological manifestation of diabetes mellitus. The formulation comprises preferably, human insulin and aloe vera. The formulations are useful for the treatment of dermatological manifestation of diabetes mellitus.

BACKGROUND OF INVENTION

Diabetes mellitus is a heterogeneous disease which leads to abnormal increase in blood glucose levels due to abnormal functioning of pancreatic beta cells. Increase in blood glucose level causes damage to wide range of cell types includes endothelial cells, neurons, renal cells, keratinocytes and fibroblasts(Abdollahi et al. 2007; Brugler et al. 2011). Chronic diabetes mellitus can cause several diabetic manifestations like diabetic neuropathy, diabetic nephropathy, diabetic myopathy, diabetic dermopathy(Mahmood and Bari 2014). Globally, various clinical studies were conducted on different population of diabetic patients and reported in the literatures. One of the studies was conducted among Sweden population and the results exhibited that 33% of the patients had diabetic dermopathy in type 1 diabetes mellitus and 39% of the patients had diabetic dermopathy in type 2 diabetes mellitus(Mahmood and Bari 2014). In Singapore, two clinical studies were reported that, 24% had diabetic dermopathy out of 135 hospitalized diabetic patients and 16% had diabetic dermopathy out of 100 outdoor diabetic patients(Morgan and Schwartz 2008). In Iran, a study was conducted on 181 outdoor diabetic patients and the results exhibited that 26% of the patient had diabetic dermopathy, 37.4% of the patient had diabetic retinopathy and 16.6% of the patients had both complications(Abdollahi et al. 2007). In Helsinki, Finland a clinical study was conducted on 750 outdoor diabetic patients and the result was reported that 6.9% of the patient had type 1 diabetes mellitus and 93% of the patient had type 2 diabetes mellitus(Emre et al.

2013). Among them 38% of the patient had diabetic neuropathy, 23.3% of the patient had diabetic nephropathy, 22.9% of the patient had diabetic retinopathy and 79.2% of the patient had diabetic dermopathy(Emre et al. 2013). Diabetic dermopathy can be recognized as skin problem having patches due to high level of blood glucose in chronic condition. It is also recognized as little flaky red or purple macule (0.5 to 1.2cm) on the upper extremities, thigh region and stomach area due to alteration of skin blood flow(Abdollahi et al. 2007; Morgan and Schwartz 2008). Extravasation of erythrocytes and invasion of lymphocytes occurred in chronic condition of diabetes mellitus(Brugler et al. 2011; Bustan et al. 2017). Existing well established hypoglycemic agents are exist for the treatment of diabetes mellitus in the form of parenteral and orally but among these insulin therapy is one of the best useful treatment for type 1 and type 2 and its diabetes complications(Bastion and Ling 2013; Tahara et al. 2012; Tambuwala et al. 2018). A drug therapy is still missing which can be used for both the treatment diabetes mellitus and diabetes dermopathy. A regular topical formulation which can be used for the treatment of dermopathy but these have limited use because most of them are not compatible with each other, show serious adverse effects and high cost(Chang et al. 2015; Lipsky and Hoey 2009). Topical formulation is specifically applicable for skin disorders. Mostly medicinal plants are widely used for skin disorder (Chang et al. 2015; Lipsky and Hoey 2009). Aloe vera (*Aloe barbadensis miller*) is a natural medicinal plant, inner gel of aloe vera is safe and non toxic according to the cosmetic ingredient review expert panel committee, aloe vera gel and extract is in the list of FDA approved ingredient(Andersen 2007; Guo and Mei 2016), it has several therapeutic effects such as immune stimulation, wound healing, anti-inflammatory, anti-bacterial, anti-viral, anti-fungal, anti-diabetic, anti-oxidant, moisturizing, anti-aging effects, anti-neoplastic activities and also significantly found to reduce the fasting blood glucose level (Habeeb et al. 2007; Hamman 2008; Surjushe, Vasani, and Saple 2008;). As it is now insulin therapy is only drug therapy which is fast relieving treatment but it is

quite unstable for long term storage. Metacresol and/or phenol is used to enhance the stability of injectable insulin formulation but these causes serious adverse effects (allergic reaction, cell death and severe cutaneous reaction) (Wheeler and Taylor 2012).

- I. Patent RU2679449 C1 11th Feb, 2019 “Method of treating defects of skin and soft tissues in patients with diabetes mellitus and method of introduction of drug there for” the group of inventions relates to medicine, namely to surgery, and can be used to treat skin and soft tissue defects in patients with diabetic foot syndrome.
- II. Patent CN108837148 A 20th Nov, 2018 “Insulin skin medication paste for diabetes and preparation method” the invention discloses a preparation method of skin medication paste for diabetes.
- III. Patent CN108465105 A 31st Aug, 2018 “Nanometer transdermal slow-release preparation based on insulin loaded on PAMAM (polyamide-amine) dendrimers and preparation method thereof” the invention discloses a noanometer transdermal slow release insulin loaded on PAMAM (polyamide amine). Insulin nano particles are loaded into a transdermal medicine administering system.
- IV. Patent CN108273042 A 31st July, 2018 “Ginsenoside-insulin nano gel as well as preparation method and application thereof” the invention discloses ginsenoside insulin nano gel for hypoglycemic effect.
- V. Patent CN108272778 A 31st July, 2018 “Transdermally delivered ursolic acid/insulin nanoscale slow-release preparation and preparation method thereof” the invention discloses a transdermal delivered of ursolic acid/insulin nano scle slow released preparation for reducing blood sugar.
- VI. Patent CN106267164 A 4th Jan, 2017 “Particle size-controllable monodisperse insulin/chitosan gel microspheres and preparation method there

- of” the invention discloses monodisperse microsphere insulin/chitosan gel (5µm to 60µm).
- VII. Patent JP2016074662 A 12th May, 2016 “Long-lasting drug release gel composition for injection and production method thereof” the invention discloses a long lasting drug release gel which consists of insulin, insulin sensitivity improving agent sulfonyl urea or their combinations.
- VIII. Patent US2016074324 A1 17th March, 2016 "Slow and controlled released liposomal gel composition comprising hypoglycemic active ingredient and method of preparing thereof" the invention discloses a slow and controlled release liposomal gel for subcutaneous administration which consists of insulin for reducing blood sugar level.
- IX. Patent WO 2009048945 A1 April 16, 2009 “Rapid mucosal gel or film insulin compositions” gel, powder, suspension, emulsions or film formulations for systemic delivery of insulin with improved stability and rapid onset of action.
- X. Patent US 20020119914 A1 August 29, 2002 “Topical applying skin disorders” The present invention discloses new uses of insulin and pancreatin. Topical insulin and pancreatin formulation use for effective treatment of skin and scalp ageing.
- XI. Patent WO 1996023522 A1 August 8, 1996 “Treatment of diabetic neuropathy” Topical use of insulin in the treatment of diabetic neuropathy in a patient.
- XII. Patent US10238686 B1 26th March, 2019 "Antimicrobial skin cream" the invention discloses a cream containing aloe vera with other ingredients like vitamin E, vitamin D, green tea, and gelatin etc. for the treatment of antimicrobial effect.
- XIII. Patent CN108938552 A 7th December 2018 "Method for preparing skin cream" the invention discloses a skin cream containing aloe vera with other

ingredients used for defying age, beautifying, protecting and whitening the skin.

- XIV. Patent US2018344783 A1 6th DEC, 2018 "Natural intra-vaginal inserts to control imbalanced pH" invention discloses gels, tablets, powders and others modalities containing aloe vera with other ingredients can be used to maintain vagina pH.
- XV. Patent US2018344625 A1 6th Dec, 2018 "Oral care products and methods" invention discloses oral care product containing aloe leaf juice with other ingredients for the treatment of xerostomia patients.
- XVI. Patent CN108865058 A 23rd November 2018 "Environmental friendly non-toxic bonding agent" the invention discloses a bonding agent containing aloe vera gel with other ingredients.
- XVII. Patent MX2017005207A 9th Nov, 2018 "Curative and control fungicide from extracts of Larrea tridentata and aloe vera" invention discloses an aloe vera extract and Larrea tridentate composition uses as cure and control from fungicides
- XVIII. Patent KR20180119189 A 2nd November 2018 "Skin moisture and anti-ageing" the invention discloses a cosmetic composition contains aloe vera extract with other ingredients for a moisturizing and anti-ageing cream.
- XIX. Patent CN108926508 A 4th April, 2018 "Whitening cream used on face and preparation method thereof" invention discloses a whitening cream containing 3.22 to 4.8 parts of aloe vera gel with other ingredients for the treatment of shrinking pores and whitening the facial skin.
- XX. Patent CN108926514 A 4th April 2018 "Pure plant anti-ageing skin-beautifying agent and preparation method thereof" invention discloses a formulation contains 10 to 15 parts of aloe vera along with other ingredients for skin ageing.

XXI. Patent JP2007254447 A 4th October, 2007 "Cosmetic lotion by the mixture of a raw leaf of aloe vera, lemon or citrus depressa extract and awamori white liquor" the invention discloses a cosmetic lotion containing awamori white liquor and aloe extract for the treatment of gentle skin.

Our Pharmaceutical topical composition of insulin with aloe vera for treating dermatological manifestation of diabetes mellitus, is fast drying and long sticking on topical skin is novel than the transdermal patch or patch for transdermal, medicated patch, gel, cream, solution, ointment, lotion, foam, powder, aerosol, spray, liquid solution & emulsion-gel formulation of the above I to XXI disclosed patents and the marketed topical formulations worldwide. The reasons are:

Our pharmaceutical topical composition of insulin with aloe vera is unique and fast prepared formulation in worldwide for treating dermatological manifestation of diabetes mellitus.

- ✚ Our Pharmaceutical topical composition of insulin with aloe vera for treating dermatological manifestation of diabetes mellitus is fast drying and long sticking on topical skin. As a result, it stayed for a long time. So, through topical skin permeation of the insulin was more.
- ✚ As our Pharmaceutical topical composition of insulin with aloe vera dried fast and long stuck on the topical skin, it could neither be easily removed nor washed by little water.
- ✚ As our Pharmaceutical topical composition of insulin with aloe vera dried fast and long stuck on the topical skin, so for the patients, the chances of removal of the formulation from the body parts are minimum while wearing their clothes.
- ✚ As our Pharmaceutical topical composition of insulin with aloe vera dried fast, stuck on the skin, stays for a long time and is non irritant, so it may be used by the patients like office working males/females during their daily

routine, dancers during performances, singers during concerts, players and athletes even while performing (except swimmers) and Police and Armed forces during their duty.

- ✚ As our Pharmaceutical topical composition of insulin with aloe vera stays for a long time on the topical skin, and the % insulin release is depend on the amount of formulation and topical skin contact time, so according to patients' requirements it can be used as safe insulin concentration.
- ✚ Any external or internal patches or tapes or any types of external covers like transdermal patches, patches of transdermal or medicated transdermal not required for sticking or denying formulation on skin.
- ✚ The *in vitro*, *ex vivo*, *in vivo* and others evaluation studies results revealed that our Pharmaceutical topical formulation of insulin is stable, is fast drying and long sticking on topical skin, is able to continuously and stably release through topical skin during a long time without irritant and allergic reaction to the skin.

So, our Pharmaceutical topical composition of insulin with aloe vera can be used as novel Pharmaceutical topical composition for treating dermatological manifestation of diabetes mellitus. As the preparation method is easy so it can easily manufacture an industrial scale at a lower cost as well as the application is easy to use so patients' acceptability will be high.

SUMMARY OF THE INVENTION:

The objective of the present invention is to provide Pharmaceutical preparation technology and method of preparation relates topical composition of insulin with aloe vera, which is fast drying and long sticking on topical skin. The formulation comprises preferably, insulin human recombinant dry powder and aloe vera. The formulations are useful for treating dermatological manifestation of diabetes mellitus.

The present invention relates topical composition of insulin with aloe vera, which is fast drying and long sticking on topical skin. The formulation comprises preferably, insulin human recombinant dry powder and aloe vera. The formulations are useful for treating dermatological manifestation of diabetes mellitus.

The present invention is to provide topical composition of insulin with aloe vera, which is fast drying and long sticking on topical skin was prepared by in two step methods. In first step insulin human recombinant dry powder prepared insulin emulsion. In 100g emulsion comprising 500mg to 5000mg dry recombinant human insulin, 5 to 30g oleic acid, 20 to 50g Tween-80, 5 to 18g polyethylene glycol-400 and sterile distilled water.

In second step topical composition of insulin with aloe vera formulation was prepared along with above insulin emulsion and other excipients. In 100g topical formulation comprising 2g to 20g above prepared insulin emulsion, 0.5 to 20g aloe vera gel, 0.5g to 5g Carbopol-934, 0.5 to 5g ethyl cellulose, 0.5 to 6g Guar gum and sterile distilled water adjusted to volume up to 100g.

In another aspect, there is provided process for the preparation of Pharmaceutical topical composition of insulin with aloe vera was prepared in two step methods.

In first step preparation method of insulin emulsion comprising steps of:

- i. Dissolve dry recombinant human insulin in sterile distilled water;
- ii. In step (i) sonicate for 30 minutes for complete dissolve;
- iii. Mixed oleic acid, tween-80 and polyethylene glycol-400;
- iv. Drop wise added insulin solution in step (iii) and continuously stirring in cold condition;
- v. Suitable and desire insulin emulsion prepared.

In second step topical formulation was prepared along with above insulin emulsion along with aloe vera gel and other excipients comprising steps of:

- i. Carbopol-934 mixed in sterile distilled water and kept for overnight to prepare colloidal solution;
- ii. Guar gum mixed in sterile distilled water and kept for overnight to prepare colloidal solution;
- iii. Ethylcellulose dissolved in ethanol;
- iv. Homogeneously mixed step (i), step (ii) and step (iii) with continuously stirring;
- v. Aloe vera gel mixed in step (iv) and continuously stirring;
- vi. Insulin emulsion mixed in step (v) and continuously stirring in cold condition;
- vii. Into suitable and desire Pharmaceutical topical composition of insulin with aloe vera was prepared for treating dermatological manifestation of diabetes mellitus.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is to provide topical composition of insulin with aloe vera, which is fast drying and long sticking on topical skin useful for treating dermatological manifestation of diabetes mellitus prepared by in two step methods. In first step insulin human recombinant dry powder prepared insulin emulsion. In 100g emulsion comprising 500mg to 5000mg dry recombinant human insulin, 5 to 30g oleic acid, 20 to 50g Tween-80, 5 to 18g polyethylene glycol-400 and sterile distilled water.

In second step topical composition of insulin with aloe vera formulation was prepared along with above insulin emulsion and other excipients. In 100g topical formulation comprising 2g to 20g above prepared insulin emulsion, 0.5 to 20g aloe vera gel, 0.5g to 5g Carbopol-934, 0.5 to 5g ethyl cellulose, 0.5 to 6g Guar gum and sterile distilled water adjusted to volume up to 100g.

In another aspect, there is provided process for the preparation of Pharmaceutical topical composition of insulin with aloe vera was prepared in two step methods.

In first step preparation method of insulin emulsion comprising steps of:

- i. Dissolve dry recombinant human insulin in sterile distilled water;
- ii. In step (i) sonicate for 30 minutes for complete dissolve;
- iii. Mixed oleic acid, tween-80 and polyethylene glycol-400;
- iv. Drop wise added insulin solution in step (iii) and continuously stirring in cold condition;
- v. Suitable and desire insulin emulsion prepared.

Step1: Composition of insulin emulsion

Ingredients	Composition
Human Insulin (Recombinant dry powder) (g)	3.63
Oleic acid(g)	9
Tween-80(g)	37.5
Polyethylene glycol-400(g)	17
Distilled sterile water(g) qs 100g i.e.	32.87
Each 1g formulation contain 36.3mg insulin i.e 1000IU, each 1IU equal to 0.0363mg recombinant insulin	

In second step topical formulation was prepared along with above insulin emulsion along with aloe vera gel and other excipients comprising steps of:

- i. Carbopol-934 mixed in sterile distilled water and kept for overnight to prepare colloidal solution;
- ii. Guar gum mixed in sterile distilled water and kept for overnight to prepare colloidal solution;
- iii. Ethylcellulose dissolved in ethanol;
- iv. Homogeneously mixed step (i), step (ii) and step (iii) with continuously stirring;
- v. Aloe vera gel mixed in step (iv) and continuously stirring;

- vi. Insulin emulsion mixed in step (v) and continuously stirring in cold condition;
- vii. Into suitable and desire Pharmaceutical topical composition of insulin with aloe vera was prepared for treating dermatological manifestation of diabetes mellitus.

Step 2: Compositions of insulin with aloe vera topical formulation

Formulation	Insulin emulsion of step 1	Aloe vera gel	Carbopol-934	Ethylcellulose	Guar gum	Distilled sterile water
Insulin emulsion topical gel with aloe vera	6g formulation (0.2178g equivalent amount insulin)	16g	1.2g	2.4g	1g	Q.S 100g

Therapeutic dose of prepared insulin with aloe vera topical formulation is 500mg. The *in vitro*, *ex vivo*, *in vivo* and others evaluation studies like viscosity test, drying time, pH, skin irritation test, stability test and other evaluation parameters and tested results revealed that our Pharmaceutical topical composition of insulin with aloe vera is stable, is fast drying and long sticking on topical skin, is able to continuously and stably release through topical skin during a long time without irritant and allergic reaction to the skin.

So, our Pharmaceutical topical composition of insulin with aloe vera can be used as novel Pharmaceutical topical composition for treating dermatological manifestation of diabetes mellitus. As the preparation method is easy so it can easily manufacture an industrial scale at a lower cost as well as the application is easy to use so patients' acceptability will be high.

We Claim:

1. A method of preparing fast drying and long sticking topical composition of insulin with aloe vera for treating dermatological manifestation of diabetes mellitus, diabetes dermopathy comprising the steps of;

- i. Dissolving 50mg to 500mg dry recombinant human insulin in sterile distilled water by sonicating for 30 minutes for complete dissolve;
- ii. Mixing 5 to 30g oleic acid, 20 to 50g Tween-80, 5 to 18g polyethylene glycol-400 and sterile distilled water;
- iii. Adding Drop wise insulin solution in step (ii) and continuously stirring in cold condition so as to obtain Suitable and desire insulin emulsion ;
- iv. Mixing 0.5g to 5g Carbopol-934 mixed in sterile distilled water and kept for overnight to prepare colloidal solution;
- v. Mixing 0.5 to 6g Guar gum and sterile distilled water adjusted to volume up to 100g, kept for overnight to prepare colloidal solution;
- vi. Dissolving 0.5 to 5g Ethylcellulose dissolved in ethanol, homogeneously mixing all Carbopol-934 , Guar gum , Ethylcellulose with continuously stirring;
- vii. Mixing 0.5 to 10g Aloe vera gel continuously stirring, Insulin emulsion mixed in step (vi) and continuously stirring in cold condition so as to obtain desired topical composition.

2. The method as claimed in claim 1, wherein the Tween-80 different graded polysorbate, non ionic surfactants, a combination of one or several.

3. A fast drying and long sticking topical composition of insulin with aloe vera for treating dermatological manifestation of diabetes mellitus prepared by claim 1-2

Dated this 1st day of May 2019



(Ashish Sharma)
Authorized Agent for the
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ABSTRACT

A PHARMACEUTICAL TOPICAL COMPOSITION AND METHOD OF PREPARATION FOR TREATING DERMATOLOGICAL MANIFESTATION OF DIABETES MELLITUS THERE OF

The present invention relates to a pharmaceutical topical composition for treating dermatological manifestation of diabetes mellitus. In this preparation method it is easy to formulate the active ingredient which comprises preferably of human insulin and aloe vera. The formulation in the invention is fast drying and long sticking on topical skin, is able to continuously and stably release human insulin through topical skin during a long time. It has good curative effect and provide both local and systemic action; is non irritant to skin, doesn't cause allergic reaction and prevents the impact on medication resulted by wearing clothes, dancing, playing, travelling, sleeping and light working.