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(72) **Inventeurs/Inventors:**
AMBULGE, JEETENDRA KASHINATH, IN;
SAVANT, DATTATRAYA APPARAO, IN;
AGRAWAL, GAURAVKUMAR RAMANLAL, IN

(73) **Propriétaire/Owner:**
WOCKHARDT LIMITED, IN

(74) **Agent:** SMART & BIGGAR

(54) **Titre : COMPOSITION COMPRENANT DE L'INSULINE ET DE L'HUILE VEGETALE POUR UNE ADMINISTRATION
TRANSDERMIQUE OU TRANSMUCOSALE**
(54) **Title: COMPOSITION COMPRISING INSULIN AND HERBAL OIL FOR TRANSDERMAL OR TRANSMUCOSAL
ADMINISTRATION**

(57) **Abrégé/Abstract:**

The invention provides an a pharmaceutical composition for transdermal or transmucosal administration comprising insulin, insulin analogues or derivatives, an effective amount of herbal oil and one or more surfactant or polymeric ingredient optionally along with one or more pharmaceutically acceptable excipients for treating diabetic disorders.

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(71) **Applicant** (for all designated States except US): **WOCK-HARDT LIMITED** [IN/IN]; D-4, MIDC Industrial Area, Chikalthana, Aurangabad 431210 (IN).

(72) Inventors; and

(75) **Inventors/Applicants** (for US only): **AMBULGE, Jee-tendra kashinath** [IN/IN]; Samyak Arcade, Flat No-D2/12, Cannaught Circle, Town Centre, CIDCO, Aurangabad 431003 (IN). **SAVANT, Dattatraya Apparao** [IN/IN]; Omkar Nivas, BH-1-52, N-2, CIDCO, Thakre Nagar, Aurangabad-431006, Maharashtra (IN). **AGRAWAL, Gauravkumar Ramanlal** [IN/IN]; At & Post: Tondapur, Tq : Jamner Dist: Jalgaon - 424207, Maharashtra, Jalgaon 424207 (IN).(81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.(84) **Designated States** (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).**Published:**

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(54) **Title:** COMPOSITION COMPRISING INSULIN AND HERBAL OIL FOR TRANSDERMAL OR TRANSMUCOSAL ADMINISTRATION(57) **Abstract:** The invention provides an a pharmaceutical composition for transdermal or transmucosal administration comprising insulin, insulin analogues or derivatives, an effective amount of herbal oil and one or more surfactant or polymeric ingredient optionally along with one or more pharmaceutically acceptable excipients for treating diabetic disorders.

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COMPOSITION COMPRISING INSULIN AND HERBAL OIL FOR TRANSDERMAL OR TRANSMUCOSAL ADMINISTRATION

Field of the Invention

The invention relates to a pharmaceutical composition for transdermal or transmucosal administration comprising insulin, insulin analogue or derivatives thereof, an effective amount of herbal oil optionally along with one or more pharmaceutically acceptable excipients. The invention further provides the process for preparing the said pharmaceutical composition.

Background of the Invention

Diabetes is a metabolic disorder wherein the human body does not produce or properly uses insulin. Diabetes affects approximately 170 million people worldwide. The two principal idiopathic forms of diabetes are known as types 1 and type 2 diabetes. Insulin injections are prescribed to the patients suffering from diabetes.

Insulin is a natural hormone, which controls the level of the sugar glucose in the blood. In healthy people, insulin is released in blood by the pancreas as the concentration of blood glucose rises. Increased blood glucose levels, occur after meals and are rapidly compensated by a corresponding increase in insulin secretion. Insulin plays major role in converting the excess blood glucose into glycogen and storing it in liver.

When insulin is absent (or low), glucose is not taken up by body cells, and the body begins to use fat as an energy source. The failure to make insulin or insufficiency of insulin is termed as Diabetes mellitus.

Traditionally short acting regular Insulin formulations or its intermediate acting Insulin Protamine formulations were used for treating patients with diabetes mellitus. With time, new insulin analogues and derivatives were developed. Insulin analogues and derivatives differ from human insulin at one or more than one amino acid positions and/or amino acid chain length.

A number of insulin, insulin analogs and derivatives are available in the market. The commonly used types of insulin, insulin analogs or insulin derivatives are categorized as:

Rapid-acting Insulin analogs: For example insulin aspart (Novolog[®]) or insulin lispro (Humalog[®]). These analogs begin to work within 5 to 15 minutes of administration and are active for 3 to 4 hours.

Short-acting insulin: For example Regular insulin (Humulin[®] or Novolin[®]). Regular insulin starts working within 30 minutes after administration and duration of action lasts from about 5 to 8 hours.

Intermediate-acting insulin: For example as Isophane insulin. It starts working in 1 to 3 hours after administration. Its duration of action varies between 16 to 24 hours.

Long-acting Insulin: For example Insulin glargine and Insulin detemir. Both these analogs starts working within 1 to 2 hours and their duration of action varies from about 12 to about 24 hours.

Mixed Insulins: For example mixture of NPH and regular insulin. There are several variations with different proportions of the mixed insulins. The onset of action of these mixed preparations is about 30 minutes.

All the available Insulin formulations are given parenterally to patients requiring frequent injections. In a recent survey conducted by University of Pennsylvania School of Medicine (Aug., 2008) on behalf of the American Association of Diabetes Educators (AADE), one-third of insulin-dependent diabetic patients said the frequent injections were a source of dread and were the hardest aspect of their diabetes care. The frequent subcutaneous or intravenous injections are associated with adverse effects as including bruises, pain, and scars as well as anxiety. Further, these methods of administration have the disadvantage that when administered, they cannot be withdrawn, e.g. in the case of development of hypoglycemia or other adverse patient reactions.

Noninvasive transdermal or transmucosal insulin delivery could not only provide diabetic patients with sustained physiological levels of basal insulin in a pain-free manner but can also be withdrawn in case of emergencies. Further, transdermal or transmucosal administration is convenient and user friendly, thus leading to patient compliance.

However, effective insulin absorption via these routes is limited for obvious reasons.

- (1) Effective delivery across the transmucosal or transdermal route is unlikely because of a high molecular weight and size of insulin.
- (2) Degradation of insulin by enzymes present in dermal layers or Buccal cavity
- (3) Low permeability of transdermal route
- (4) Limited stability of peptides during preparation of formulation and storage
- (5) Intra-individual variability, etc.

Attempts have been made to develop transdermal and transmucosal insulin formulations usually involving additional excipients such as use of lipophilic compounds such as triglycerides, penetration enhancers, etc or delivery methods or devices iontophoresis, use of thermal energy, ultrasound etc. to achieve desired absorption.

US Patent No. 5,707,641 US Patent No. 7,033,998 and US 7,291,591 disclose pharmaceutical formulations for transdermal administration.

US Patent No. 5,597,796, US Patent No. 6,002,961, US Patent No. 5,814,599 and US Patent No. 6,190,315 disclose transdermal delivery of insulin or its analogues using iontophoresis or sonophoresis.

US Patent No. 6,274,166 discloses transdermal delivery system comprising an active ingredient selected from the group consisting of peptides, proteins and mixtures thereof and a pharmaceutically acceptable oxidizing agent.

US Patent No. 5,932,240 disclose multidose transdermal drug delivery assembly, wherein unit doses being in the form of a multiphase composition of microspheres.

US Patent No. 6,998,110, US Patent Application No. 20100034880, US Patent Application No. 20090274758, IN Patent Application No. 2004MU00681 and PCT Patent Application No. 2008127679 disclose compositions comprising peptide drugs for transmucosal administration.

Use of synthetic excipients or artificial methods for delivery of insulin, insulin analogue or derivatives, are associated with number of immunogenic reactions and disturbances in normal physiological conditions of a body. Thus, there is a need of a system or composition, which should be less immunogenic on one hand and on other hand results in achieving desired insulin levels from non-invasive methods of delivery.

Summary of the Invention

One of the embodiments of the invention provides a pharmaceutical composition comprising insulin, insulin analogue or derivatives thereof, an effective amount of herbal oil optionally along with one or more pharmaceutically acceptable excipients.

The term "insulin" used herein includes mammalian insulin, insulin analogues or derivatives.

By "insulin analogue" (and similar expressions) as used herein is meant human insulin in which one or more amino acids have been deleted and/or replaced by other amino acids, including non-codeable amino acids, or human insulin comprising additional amino acids, i.e. more than 51 amino acids. Examples of insulin analogues are analogues of human insulin where the amino acid residue at position B28 is Asp, Lys, Leu, Val, or Ala and position B29 is Lys or Pro; or B3 is Lys and B29 is Glu; or A21 is Gly and Arg has been added to B31 and B32; or where the amino acid residues in B28-B30 have been deleted; or where the amino acid residue at B27 has been deleted; or where the amino acid residue at B30 has been deleted. Marketed Insulin analogues include but are not limited to Insulin aspart, Insulin Lispro, Insulin glulisine, Insulin glargine, etc.

By "insulin derivative" (and similar expressions) as used herein is meant human insulin or an analogue thereof in which at least one organic substituent is bound to one or more of the amino acids. Non-limiting examples of a "insulin derivative" are B29-N^ε-myristoyl-des(B30) human insulin (Insulin detemir), B29-N^ε-palmitoyl-des(B30) human insulin, B29-N^ε-myristoyl human insulin, B29-N^ε-palmitoyl human insulin, B28-N^ε-myristoyl Lys^{B28}Pro^{B29} human insulin, B28-N^ε-palmitoyl Lys^{B28}Pro^{B29} human insulin, B30-N^ε-myristoyl-Thr^{B29}Lys^{B30} human insulin, B30-

N^ε-palmitoylThr^{B29}Lys^{B30} human insulin, B29-N^ε-(N-palmitoyl-γ-glutamyl)-des(B30) human insulin, B29-N^ε-(N-lithocholyl-γ-glutamyl)-des(B30) human insulin, B29-N^ε-(ω-carboxyheptadecanoyl)des(B30) human insulin and B29-N^ε-(ω-carboxyheptadecanoyl) human insulin.

Non-limiting examples of Insulin, Insulin analogue and derivatives includes Recombinant human insulin, Insulin NPH, Insulin Lispro, Insulin Lispro Protamine, Insulin Glulisine and Insulin Aspart, Insulin Aspart Protamine, Insulin glargine, insulin detemir or mixtures thereof.

One of the other embodiment of the present invention provides a pharmaceutical composition for transdermal or transmucosal administration comprising insulin, insulin analogue or derivatives thereof, an effective amount of herbal oil optionally along with one or more pharmaceutically acceptable excipients.

Another embodiment of the present invention provides a pharmaceutical composition for transdermal or transmucosal administration comprising insulin, insulin analogue or derivatives thereof, an effective amount of herbal oil optionally along with one or more pharmaceutically acceptable excipients, wherein the said insulin, insulin analogue or derivative has not been subjected to any pretreatment.

Another embodiment of the present invention provides a pharmaceutical composition for transdermal or transmucosal administration comprising insulin, insulin analogue or derivatives thereof, an effective amount of herbal oil optionally along with one or more pharmaceutically acceptable excipients, wherein the composition when administered by the said routes, insulin is detectable in blood in less than 1h after administration.

Yet another embodiments of the present invention provides a method for treating diabetes by administering a pharmaceutical composition comprising insulin, insulin analogue or derivatives thereof, an effective amount of herbal oil optionally along with one or more pharmaceutically acceptable excipients to a patient in need thereof.

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In a claimed embodiment, the present invention relates to a pharmaceutical composition for transdermal or transmucosal administration consisting of insulin, an insulin analogue, or an insulin derivative; an herbal oil extracted from a plant species selected from the group consisting of brassica junecea, pinus, mentha and ricinus; and one or more polymeric ingredients along with one or more pharmaceutically acceptable excipients, wherein the one or more polymeric ingredients include a natural gum selected from the group consisting of xanthan gum, gum acacia, tragacanth gum, karaya gum, gum arabic, locust bean gum, gellan gum and sodium alginate.

In a claimed embodiment, the present invention relates to a pharmaceutical composition for transdermal or transmucosal administration consisting of insulin, an insulin analogue, or an insulin derivative; an herbal oil extracted from a plant species selected from the group consisting of brassica junecea, pinus, mentha and ricinus; and one or more polymeric ingredients along with one or more pharmaceutically acceptable excipients, wherein the one or more polymeric ingredients include a natural gum selected from the group consisting of xanthan gum, gum acacia, tragacanth gum, karaya gum, gum arabic, locust bean gum, gellan gum and sodium alginate, and wherein the insulin, the insulin analogue or the insulin derivative in the composition is not subjected to any pretreatment.

In a claimed embodiment, the present invention relates to a pharmaceutical composition for transdermal or transmucosal administration consisting of insulin, an insulin analogue, or an insulin derivative; an herbal oil extracted from a plant species selected from the group consisting of brassica junecea, pinus, mentha and ricinus; and one or more polymeric ingredients along with one or more pharmaceutically acceptable excipients, wherein the one or more polymeric ingredients include a natural gum selected from the group consisting of xanthan gum, gum acacia, tragacanth gum, karaya gum, gum arabic, locust bean gum, gellan gum and sodium alginate, and wherein when the composition is administered, the insulin, the insulin analogue, or the insulin derivative is detectable in blood in less than 1h after administration.

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One of the embodiments of the pharmaceutical composition may include one or more of the following features. The pharmaceutical composition may further comprises one or more pharmaceutically acceptable excipients selected from the group consisting of polymeric ingredient, surfactant, emulsifiers, penetration enhancers, surfactants, pH modifiers or buffering agents, thickening or gelling agents, stabilizing agents, antimicrobials and preservatives.

Description of drawings

Figure 1 depicts the photomicrographs of the composition of Table 1 at magnification of 100X oil immersion. Small globules entrapping Insulin were prominently visible.

Figure 2 graphically compares the results of a biostudies in which compositions according to embodiments of the invention were administered transdermally and marketed regular insulin compositions were administered subcutaneously to healthy Wistar rats.

Detailed Description of the Invention

While working on development of compositions comprising insulin, insulin analog and derivatives suited specially for non-invasive routes such as transdermal or transmucosal routes, inventors have surprising found that when herbal oil is added to insulin solution slowly using trituration or sonication technique the resulting composition comprising numerous small globules entrapping insulin, which when applied on skin results in rapid systemic absorption, i.e. less than 1h, of insulin across skin. The composition was found to be stable.

In one of the embodiments of the present invention, herbal oil can be extracted from the herbs selected from the group consisting of extracted and processed from brassica juncea, pinus, mentha and ricinus species. The invention is not limited to the examples, it encompass all the possible related species envisioned by a person ordinary skilled in the art.

In one of the embodiments of the present invention, one or polymeric ingredient includes natural gums selected from the group consisting of Xanthan gum, Gum acacia, Tragacanth gum, Karaya gum, Gum Arabic, Locust bean gum, Gellan gum and Sodium alginate.

Suitable surfactants are those known to ordinary skilled in the art and may include one or more of amphoteric, non-ionic, cationic or anionic surfactants. Suitable surfactants comprises one or more of sodium lauryl sulfate, monooleate, monolaurate, monopalmitate, monostearate or another ester of polyoxyethylene sorbitane, sorbitan monostearate, sodium dioctylsulfosuccinate (DOSS), lecithin, stearyl alcohol, cetostearyl alcohol, cholesterol, polyoxyethylene ricin oil, polyoxyethylene fatty acid glycerides, poloxamer, or cremophore RH 40.

Emulsifiers include one or more of alkyl alcohols, alkyl polyglucosides, polyglycerol alkyl esters, C1-C4 esters of alkyl alcohols, C1-C4 esters of alkyl carboxylates, alkyl amides, alkyl betaines, and alkyl phosphates or phospholipids, alkyl quaternary amines, alkyl amine oxides, polyethoxylated alkyl alcohols, alkyl esters of polyethylene glycol, and mixtures thereof.

Penetration enhancers can be selected from the group consisting of C₈-C₂₂ fatty acids such as isostearic acid, octanoic acid, and oleic acid, C₈-C₂₂ fatty alcohols such as oleyl alcohol and lauryl alcohol, lower alkyl esters of C₈-C₂₂ fatty acids such as ethyl oleate, isopropyl myristate, butyl stearate, and methyl laurate, di(lower)alkyl esters of C₆ -C₈ diacids such as diisopropyl adipate, monoglycerides of C₈-C₂₂ fatty acids such as glyceryl monolaurate, tetrahydrofurfuryl alcohol polyethylene glycol ether, polyethylene glycol, propylene glycol, 2-(2-ethoxyethoxy)ethanol, diethylene glycol monomethyl ether, alkylaryl ethers of polyethylene oxide, polyethylene oxide monomethyl ethers, polyethylene oxide dimethyl ethers, dimethyl sulfoxide, glycerol, ethyl acetate, acetoacetic ester, N-alkylpyrrolidone, and terpenes.

Suitable thickening agents, viscosity modifiers or gelling agents can be selected from the group consisting carbomer, carboxyethylene or polyacrylic acid such as Carbopol 980 or 940 NF, 981 or 941 NF, 1382 or 1342 NF, 5984 or 934 NF, ETD 2020, 2050, 934P NF, 971P NF, 974P NF, Noveon AA-1 USP, etc; cellulose derivatives such as methylcellulose, ethylcellulose,

hydroxypropylmethylcellulose (HPMC), ethylhydroxyethylcellulose (EHEC), carboxymethylcellulose (CMC), hydroxypropylcellulose (HPC) (Klucel different grades), hydroxyethylcellulose (HEC) (Natrosol grades), HPMCP 55, Methocel grades, etc; natural gums such as arabic, xanthan, guar gums, alginates, etc; polyvinylpyrrolidone derivatives such as Kollidon grades; polyoxyethylene polyoxypropylene copolymers such as Lutrol F grades 68, 127, etc; chitosan, polyvinyl alcohols, bentonite, hectorite, pectins, maltitol, and veegun grades.

Suitable pH modifiers or buffering agents may include one or more of a bicarbonate salt of a Group IA metal, an alkali earth metal buffering agent, a calcium buffering agent, a magnesium buffering agent, an aluminum buffering agent and the like, sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium gluconate, magnesium oxide, magnesium aluminate, magnesium carbonate, magnesium silicate, magnesium citrate, aluminum hydroxide, aluminum phosphate, aluminum hydroxide/magnesium carbonate, potassium carbonate, potassium citrate, aluminum hydroxide/sodium bicarbonate coprecipitate, aluminum glycinate, aluminum magnesium hydroxide, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium (polyphosphate, sodium dihydrogen phosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, potassium metaphosphate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium gluconate, calcium bicarbonate, calcium citrate, calcium phosphate magnesium phosphate, potassium phosphate, sodium phosphate, trihydroxymethylaminomethane, amino acid, an acid salt of an amino acid, an alkali salt of an amino acid, and combinations of any of the foregoing.

Moreover, the composition of the invention optionally include usual auxiliaries known in the art such as saliva stimulating agents like citric acid, lactic acid, malic acid, succinic acid, ascorbic acid, adipic acid, fumaric acid, tartaric acids; cooling sensation agents like maltitol, monomethyl succinate, ultracool; stabilizers like gums, agar; taste masking agents like acrylic polymers, copolymers of acrylates, celluloses, resins; zinc, coloring agents like titanium dioxide, natural food colors, dyes suitable for food, drug and cosmetic applications;

preservatives like alpha-tocopherol, citric acid, butylated hydroxytoluene, butylated hydroxyanisole, ascorbic acid, fumaric acid, malic acid, sodium ascorbate or ascorbic acid palmitate or effervescing agents like citric acid, tartaric acid, sodium bicarbonate, sodium carbonate and the like.

Preservatives or antimicrobials may include one or more of sodium benzoate, sorbates, such as potassium sorbate, salts of edetate (also known as salts of ethylenediaminetetraacetic acid or EDTA, such as disodium edetate), benzaldionium chloride, parabens, iodine and its complexed forms such as povidone/iodine, chlorhexidine salts such as chlorhexidine digluconate (CHG), parachlorometaxylenol (PCMX), hexachlorophene, phenols, hydrogen peroxide, phenols, silver, silver salts such as silver chloride, silver oxide and silver sulfadiazine and the like.

The propellant can be chosen from chlorofluorocarbons (CFCs), hydrochlorofluorocarbons (HCFCs), hydrofluorocarbons (HFCs), perfluorinated alkanes, and lower alkanes (C1-C5) as well as nitrous oxide, dimethyl ether, and other solvent-soluble propellants

In one of the embodiments of the present invention, the pharmaceutical composition is an emulsion, dispersion, suspension, film or patch.

In another embodiment of the present invention, the pharmaceutical composition is an emulsion, dispersion or suspension.

In another embodiment of the invention, the pH of the composition is from about 4.5 to about 7.5.

The pharmaceutical compositions of the present invention can be prepared by the various processes known in the art.

Example 1

Table 1: Insulin Composition

Sr. No.	Ingredients	Quantity (% w/v or v/v)
1	Recombinant Human Insulin	0.1 - 1.0%
2	Xanthan Gum	1.0 - 4.0%
3	Herbal Oil	30 - 50%
4	Purified Water	30 - 50%

Procedure - Xanthan Gum was weighed accurately in requisite amount and dissolved in herbal oil using mortar & pestle. Accurately weighed recombinant human insulin or insulin analogs was transferred to the above solution in mortar and pestle and mixed slowly with oil phase for 5 - 30 min under cold temperature (2-8°C). An equal amount of water was added drop wise to the mortar and pestle under constant mixing for 20 - 90 min to prepare a homogeneous suspension.

Example 2

For stability studies, the vials containing Insulin composition of Table 1 were stored at a temperature between 2°C to 8°C for a period of three month. The potency of insulin was measured by conducting assay using standard procedure for assaying under insulin human as per USP31 NF26. The limit for related impurities like A-21 desamido was carried out using standardized procedure mentioned in USP31 NF26. The assay and test for detecting limit for related impurities like A-21 desamido were conducted before the initiation of storage, and after 3 months further studies. The results are shown in Table 2.

Table 2 – Stability data comparison when the composition of Table 1 is subjected to stability studies.

S. No.	Parameters	Limits	Initial	3 months
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1.	Description	A brownish suspension	A brownish suspension	A brownish suspension
2.	pH	Between 4.5 and 7.5	5.86	5.91
3.	Related impurities A21 desamido	NMT 5%	1.95 %	1.84 %
4.	Concentration of Insulin	Between 9.0 mg to 11.0 mg per ml	10.86 mg/ml	10.07 mg/ml

As is clear from Table 2, when the composition of this invention was stored at a temperature of 2°C to 8°C, it was found to be stable for 3 month. The composition did not changed in appearance and was found to be devoid of related A21 desamido impurities. The active ingredient recombinant human insulin has not degraded during storage.

Example 3

For in vivo studies, wistar rats were fasted overnight prior to the experiment but had free access to water during the study. A total of 06 wistar rats (250–300 g) were divided in two experimental groups “A” and “B” with three rats in each group. Pharmaceutical composition prepared according to one of the embodiments of the invention comprising 40IU was applied on shaved skin of rats of group A for transdermal administration. Regular insulin marketed composition (Wosulin®) comprising 1IU insulin was administered subcutaneously to rats of group B. Blood samples were withdrawn at an interval of 1h, 2.5h and 5h after administration. The results of biostudy were represented in Figure 2.

Around 60% reduction in the blood glucose level was observed within one hour after the transdermal application insulin compositions according to present invention in rats. The effect of reduction in blood glucose level in rat persisted till 3-4 hours after transdermal administration whereas on other hand reduction in blood glucose level after subcutaneous injection under the same conditions persisted for 2-3 hours with 57% reduction in blood glucose level.

Figure 1 depicts the photomicrographs of the composition of Table 1 at magnification of 100X oil immersion. Small globules entrapping Insulin were prominently visible.

Figure 2 graphically compares the results of a biostudies in which compositions according to embodiments of the invention were administered transdermally and marketed regular insulin compositions were administered subcutaneously to healthy Wistar rats.

Example 4

Table 3: Insulin Composition

Sr. No.	Ingredients	Quantity
1	Insulin Human (Recombinant DNA Origin)	0.1 - 1.0% w/v
2	Sorbitan Monostearate (Span 60)	1.0 - 5.0% w/v
3	Herbal Oil	30 - 50% v/v
4	Purified Water	30 - 50% v/v

Procedure - Sorbitan Monostearate (Span 60) was weighed accurately in requisite amount and dissolved in herbal oil using mortar & pestle. Accurately weighed recombinant human insulin or insulin analogs was transferred to the above oily solution in mortar and pestle and mixed slowly with oil phase for 5 - 30 min under cold temperature (2-8°C). An equal amount of water was added drop wise to the mortar and pestle under constant mixing for 20 - 90 min to prepare a homogeneous suspension.

Example 5

For stability studies, the vials containing Insulin composition of Table 3 were stored at a temperature between 2°C to 8°C for a period of three month. The potency of insulin was measured by conducting RP-HPLC method for assay given in monograph entitled "Insulin Human" as per USP32 NF27. Stability testing parameters like Description, pH, Assay of Insulin Human & Viscosity (using Brookfield Viscometer) were determined and recorded

before the initiation of stability study (Storage Conditions: $5^{\circ} \pm 3^{\circ}\text{C}$), and also after 3 months of storage at specified conditions. The results are shown in Table 4.

Table 4 – Stability data comparison when the composition of Table 3 is subjected to stability studies.

<u>Tests</u>	Acceptance Criteria	Results	
		Initial	3rd Month
Description	A brownish suspension, traces of fine sediment may be deposited.	A brownish suspension, traces of fine sediment may be deposited.	A brownish suspension, traces of fine sediment may be deposited.
pH	Between 4.5 and 7.5	5.81	5.86
Assay of Insulin Human	Not less than 80% and not more than 120% of label claim	108.65%	100.75%
Viscosity	Not less than 30 cP and not more than 50 cP.	37.3 cP	38.5 cP

As is clear from Table 4, when the composition of this invention was stored at a temperature of 2°C to 8°C , it was found to be stable for 3 month. The composition did not changed in appearance. The active ingredient recombinant human insulin has not degraded during storage.

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

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CLAIMS:

1. A pharmaceutical composition for transdermal or transmucosal administration consisting of insulin, an insulin analogue, or an insulin derivative; an herbal oil extracted from a plant species selected from the group consisting of brassica junecea, pinus, mentha and
5 ricinus; and one or more polymeric ingredients along with one or more pharmaceutically acceptable excipients, wherein the one or more polymeric ingredients include a natural gum selected from the group consisting of xanthan gum, gum acacia, tragacanth gum, karaya gum, gum arabic, locust bean gum, gellan gum and sodium alginate.
2. The pharmaceutical composition as claimed in claim 1, wherein the insulin, the
10 insulin analogue or the insulin derivative is selected from the group consisting of recombinant human insulin, insulin NPH, insulin aspart, insulin lispro, insulin glulisine, insulin glargine and insulin derivative.
3. The pharmaceutical composition of claim 1 or 2, wherein the one or more pharmaceutically acceptable excipients is selected from the group consisting of a surfactant, a
15 buffer, a complexing agent, a stabilizer, a pH adjusting agent, a gelling agent, an antioxidant and a preservative.
4. The pharmaceutical composition as claimed in claim 3, wherein the surfactant is an amphoteric, a non-ionic, a cationic or an anionic surfactant.
5. The pharmaceutical composition of any one of claims 1 to 4, wherein the
20 pharmaceutical composition is an emulsion, a dispersion, a suspension, a buccal film, a transdermal film, or a patch.
6. A pharmaceutical composition for transdermal or transmucosal administration consisting of insulin, an insulin analogue, or an insulin derivative; an herbal oil extracted from a plant species selected from the group consisting of brassica junecea, pinus, mentha and
25 ricinus; and one or more polymeric ingredients along with one or more pharmaceutically acceptable excipients, wherein the one or more polymeric ingredients include a natural gum selected from the group consisting of xanthan gum, gum acacia, tragacanth gum, karaya gum,

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gum arabic, locust bean gum, gellan gum and sodium alginate, and wherein the insulin, the insulin analogue or the insulin derivative in the composition is not subjected to any pretreatment.

7. The pharmaceutical composition as claimed in claim 6, wherein the insulin, the insulin analogue or the insulin derivative is selected from the group consisting of recombinant human insulin, insulin NPH, insulin aspart, insulin lispro, insulin glulisine, insulin glargine and insulin derivative.

8. The pharmaceutical composition of claim 6 or 7, wherein the one or more pharmaceutically acceptable excipients is selected from the group consisting of a surfactant, a buffer, a complexing agent, a stabilizer, a pH adjusting agent, a gelling agent, an antioxidant and a preservative.

9. The pharmaceutical composition as claimed in claim 8, wherein the surfactant is an amphoteric, a non-ionic, a cationic or an anionic surfactant.

10. A pharmaceutical composition for transdermal or transmucosal administration consisting of insulin, an insulin analogue, or an insulin derivative; an herbal oil extracted from a plant species selected from the group consisting of brassica juncea, pinus, mentha and ricinus; and one or more polymeric ingredients along with one or more pharmaceutically acceptable excipients, wherein the one or more polymeric ingredients include a natural gum selected from the group consisting of xanthan gum, gum acacia, tragacanth gum, karaya gum, gum arabic, locust bean gum, gellan gum and sodium alginate, and wherein when the composition is administered, the insulin, the insulin analogue or the insulin derivative is detectable in blood in less than 1h after administration.

11. The pharmaceutical composition as claimed in claim 10, wherein the insulin, the insulin analogue or the insulin derivative is selected from the group consisting of recombinant human insulin, insulin NPH, insulin aspart, insulin lispro, insulin glulisine, insulin glargine and insulin derivative.

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12. The pharmaceutical composition of claim 10 or 11, wherein the one or more pharmaceutically acceptable excipients is selected from the group consisting of a surfactant, a buffer, a complexing agent, a stabilizer, a pH adjusting agent, a gelling agent, an antioxidant and a preservative.

5 13. The pharmaceutical composition according to any one of claims 1 to 12, for use in the treatment of diabetes.

FIGURE 1(A): PHOTOMICROGRAPH OF INSULIN COMPOSITION

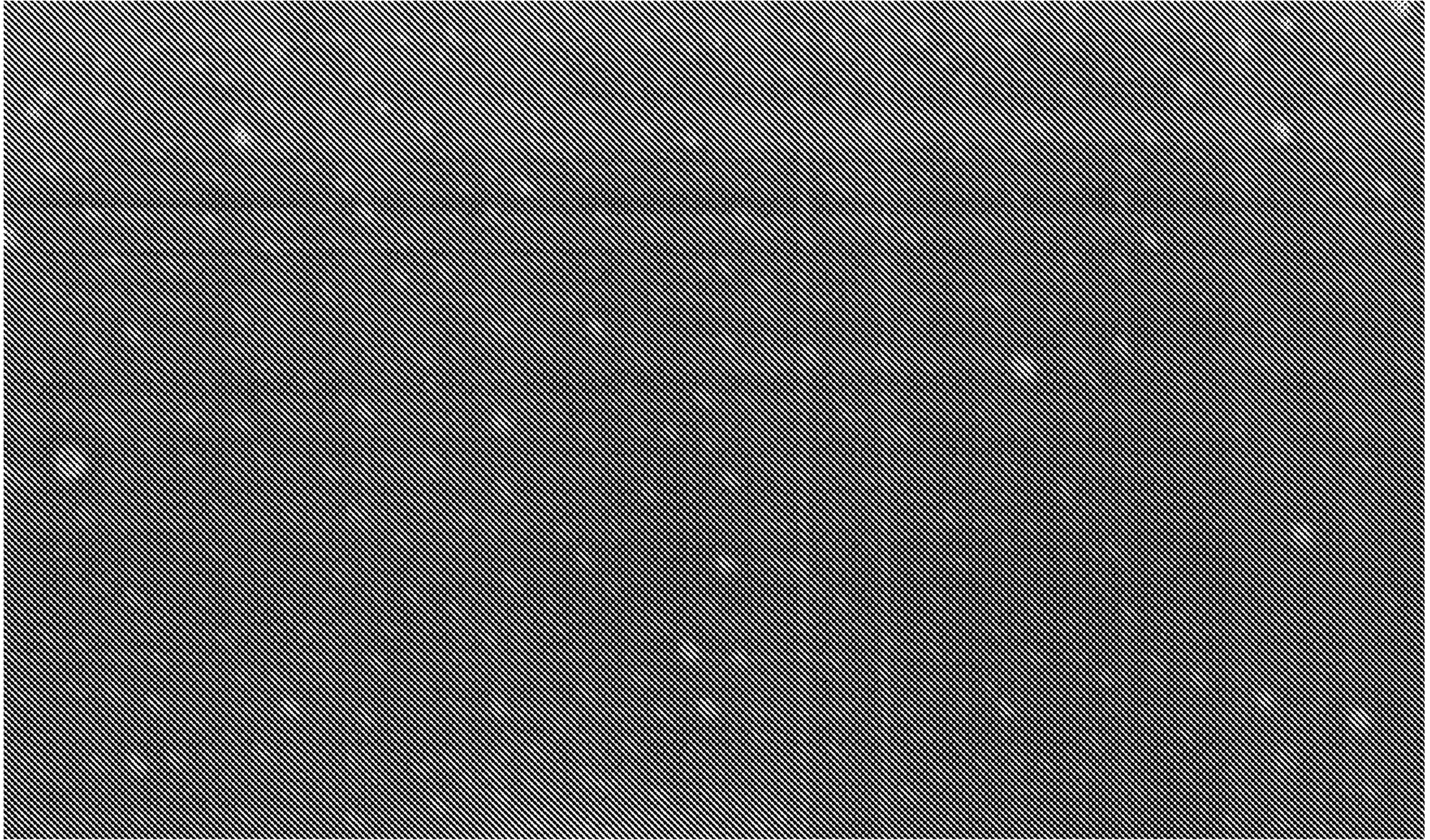


FIGURE 1(B): PHOTOMICROGRAPH OF INSULIN COMPOSITION

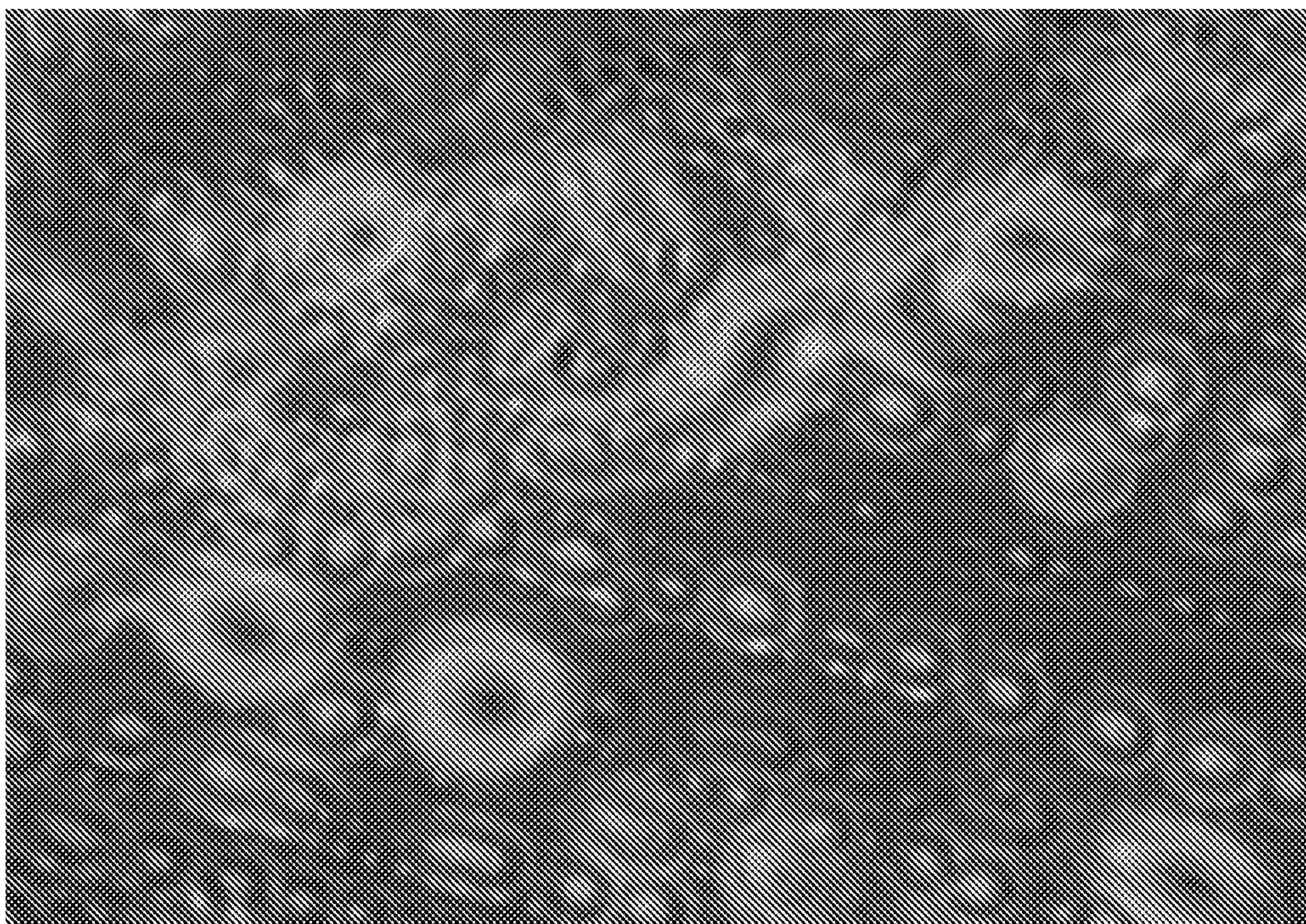


FIGURE 2: COMPARATIVE BLOOD GLUCOSE LEVELS AFTER TRANSDERMAL AND SUBCUTANEOUS INSULIN ADMINISTRATION

