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FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES BY USING MEDICINAL PLANT (NEEM) IN THE TREATMENT OF DIABETES

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ABSTRACT

Diabetes is a common disorder that is related to the loss of insulin or Pancreas is unable to make sufficient insulin for the body and this can belong to any age group. Diabetes is a chronic metabolic disease and it has been recognized for more than 1550BC, is an important problem in primary health care practices. The Present work is done by formulating and evaluating Transdermal patches by using Medicinal Herbal Plant (Neem). The Formulation was evaluated for physical parameter like pH, stability study, Percent moisture absorption, Percent moisture loss, Thickness, Weight variation, Folding endurance, Drug content. The Formula was evaluated in colour, odour, visual appearance, foreign particle, Thickness.

KEYWORDS: Diabetes, Insulin, Transdermal Patch, Skin.

1. INTRODUCTION

Diabetes mellitus, often known simply as diabetes, is a group of common endocrine diseases characterized by sustained high blood sugar levels. Diabetes is due to either the pancreas not producing enough insulin, or the cells of the body becoming unresponsive to the hormone's effects. Classic symptoms include thirst, polyuria, weight loss, and blurred vision. If left untreated, the disease can lead to various health complications, including disorders of the cardiovascular system, eye, kidney, and nerves. Untreated or poorly treated diabetes accounts for approximately 1.5 million deaths every year.

The major types of diabetes are type 1 and type 2, though other forms also exist. The most common treatment for type 1 is insulin replacement therapy (Insulin injections), while anti-diabetic medications (Such as Metformin and Semaglutide) and lifestyle modifications can be used to manage type 2. Gestational diabetes, a form that arises during pregnancy in some women, normally resolves shortly after delivery.

As of 2021, an estimated 537 million people had diabetes worldwide accounting for 10.5% of the adult population, with type 2 making up about 90% of all cases. It is estimated that by 2045, approximately 783 million adults, or 1 in 8, will be living with diabetes, representing a 46% increase from the current figures. The prevalence of the disease continues to increase, most dramatically in low- and middle-income nations. Rates are similar in women and men, with diabetes being the seventh leading cause of death globally. The global expenditure on diabetes-related healthcare is an estimated US$760 billion a year.

The classic symptoms of untreated diabetes are polyuria, thirst, and weight loss. Several other non-specific signs and symptoms may also occur, including fatigue, blurred vision, and genital itchiness due to Candida infection. About half of affected individuals may also be asymptomatic. Type 1 presents abruptly following a pre-clinical phase, while type 2 has a more insidious onset; patients may remain asymptomatic for many years.

Diabetic ketoacidosis is a medical emergency that occurs most commonly in type 1, but may also occur in type 2 if it has been longstanding or if the individual has significant β-cell dysfunction. Excessive production of ketone bodies leads to signs and symptoms including nausea, vomiting, abdominal pain, the smell of acetone in the breath, deep breathing known as Kussmaul breathing, and in severe cases decreased level of consciousness. Hyperosmolar hyperglycemic state is another emergency characterised by dehydration secondary to severe hyperglycaemia, with resultant hypernatremia leading to an altered mental state and possibly coma.

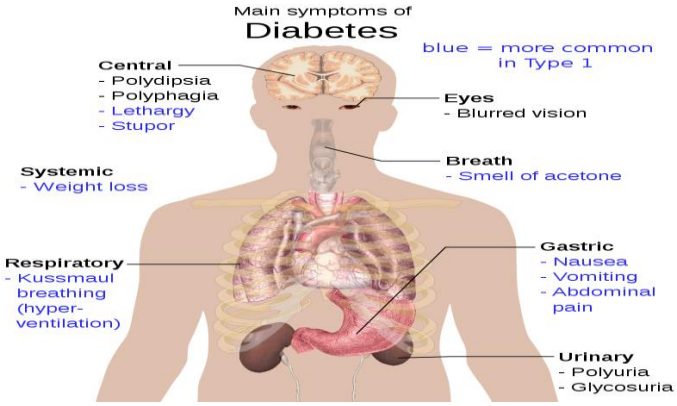

Figure 1: Patient suffering from diabetes.

Hypoglycaemia is a recognised complication of insulin treatment used in diabetes. An acute presentation can include mild symptoms such as sweating, trembling and palpitations, to more serious effects including impaired cognition, confusion, seizures, coma, and rarely death. Recurrent hypoglycaemic episodes may lower the glycaemic threshold at which symptoms occur, meaning mild symptoms may not appear before cognitive deterioration begins to occur.

In 2014, 8.5% of adults aged 18 years and older had diabetes. In 2019, diabetes was the direct cause of 1.5 million deaths and 48% of all deaths due to diabetes occurred before the age of 70 years. Another 460 000 kidney disease deaths were caused by diabetes, and raised blood glucose causes around 20% of cardiovascular deaths.

Between 2000 and 2019, there was a 3% increase in age-standardized mortality rates from diabetes. In lower-middle-income countries, the mortality rate due to diabetes increased 13%. By contrast, the probability of dying from any one of the four main noncommunicable diseases (Cardiovascular diseases, cancer, chronic respiratory diseases or diabetes) between the ages of 30 and 70 decreased by 22% globally between 2000 and 2019.

Types of diabetes

Type 1

Type 1 accounts for 5 to 10% of diabetes cases and is the most common type diagnosed in patients under 20 years, however, the older term "juvenile-onset diabetes" is no longer used as the disease not uncommonly has onset in adulthood. The disease is characterized by loss of the insulin-producing beta cells of the pancreatic islets, leading to severe insulin deficiency, and can be further classified as immune-mediated or idiopathic (Without known cause). The majority of cases are immune-mediated, in which a T cell-mediated autoimmune attack

causes loss of beta cells and thus insulin deficiency.[44] Patients often have irregular and unpredictable blood sugar levels due to very low insulin and an impaired counter-response to hypoglycaemia.

Type 2

Type 2 diabetes is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion. The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. Diabetes mellitus cases due to a known defect are classified separately. Type 2 diabetes is the most common type of diabetes mellitus accounting for 95% of diabetes. Many people with type 2 diabetes have evidence of prediabetes (Impaired fasting glucose and/or impaired glucose tolerance) before meeting the criteria for type 2 diabetes. The progression of prediabetes to overt type 2 diabetes can be slowed or reversed by lifestyle changes or medications that improve insulin sensitivity or reduce the liver's glucose production.

Skin

The membranes lining the body's orifices extend the skin's covering of the entire body,

- It protects the underlying structures from harm and from microbial invasion.
- It has somatic (Pain, Temperature and Touch) nerve endings.
- It has a role in controlling body temperature.

Structure of the skin

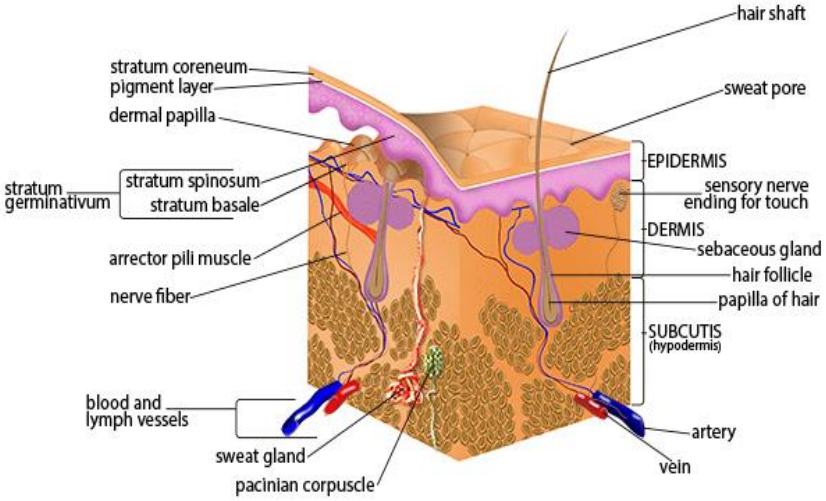

Fig. No. 2: Structure of skin.

15% of the total weight of an adult, the skin is the biggest organ in the human body. One of the easiest areas of the body to apply topical medications to is the skin. There are three main pathways by which molecules enter the skin: the intact stratum corneum, the sebaceous follicle, and the sweat ducts. At 15% of the total weight of an adult, the skin is the biggest organ in the human body. One of the easiest areas of the body to apply topical medications to is the skin. There are three main pathways by which molecules enter the skin: the intact stratum corneum, the sebaceous follicle, and the sweat ducts.

Topical channels such as the skin, eyes, rectal, and vaginal are employed in the topical medication delivery strategy to achieve localized action on the body.

The skin carries out several vital tasks, including

- Defense against attackers that use physical, biological, or chemical means
- Prevents the body from losing too much water;
- Plays a crucial part in thermoregulation;
- An enzyme in the epidermis can denature medications

The epidermis, dermis, and subcutaneous tissue are the three layers that make up the skin. For every square centimeter of skin on an average individual, there are between 40 and 70 hair follicles and 200 and 300 sweat ducts. The average adult's skin has a surface area of around 2 m^2 and gets approximately one third of the blood that circulates through the body. The pH of the skin ranges from 4 to 5.6.

Symptoms of diabetes

- Urinating more: You might urinate more often than usual, especially at night.
- Thirst: Your body is dehydrated from the extra sugar and fluids being removed from your tissues, so you might feel very thirsty.
- Tiredness: You might feel more tired than usual.
- Weight loss: Type 1 diabetes can cause unexplained weight loss, while type 2 diabetes can cause gradual weight gain.
- Blurred vision: The lens of your eye can become dry, causing blurred vision.
- Slow healing: Cuts and wounds might take longer to heal.
- Itchy skin: You might experience itchy skin or skin infections, especially around your genitals.
- Numbness or tingling: You might experience numbness or tingling in your hands or feet.

1.1.Transdermal drug delivery system

(TDDS) are described as discrete, self-contained dosage forms that, when applied to intact skin, allow the drug(s) to be delivered to the systemic circulation at a controlled pace through the skin. For strong, low-molecular-weight medicinal medicines that are either too sensitive to the harsh conditions of the gastrointestinal tract or are heavily prone to first-pass metabolism by the liver, transdermal drug delivery is a feasible mode of administration.

Fig. No. 3: Transdermal patch.

Transdermal drug delivery systems are topically applied medications in the form of patches that distribute medications at a predefined, regulated rate for systemic effects. An alternative method of delivering medication is offered by a transdermal drug delivery device, which can have an active or passive design. Pharmaceuticals can now be administered across the skin barrier thanks to these devices.

Basic components of transdermal drug delivery systems

1. Polymer matrix or matrices
2. The drug
3. Permeation enhancers
4. Other excipients

1. Polymer matrix

The Polymer controls the diffusion of the drug from the device. Possible useful polymers for transdermal devices are:

a. Natural polymers: e.g., cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch etc.

b. Synthetic elastomers: e.g., polybutadieine, Hydrin rubber, Polysiloxane,Silicone rubber,

Nitrile, Acrylonitrile, Butyl rubber, Styrenebutadieine rubber, Neoprene etc.

c. **Synthetic polymers:** e.g., polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinyl pyrrolidone, Polymethyl methacrylate, Epoxy etc.

2. Drug

The medicine must be carefully chosen in order to build a transdermal drug delivery system that works.

Some of the desired characteristics of a medication for transdermal distribution are listed below.

Physicochemical properties

- The medication's molecular weight should be less than about 1000 Daltons.
- The medication needs to be affinities for hydrophilic and lipophilic phases. Severe partitioning features are incompatible with effective topical medication administration.
- The medication's melting point need to be low.
- The medication should also have a short half-life, be non-irritating, and be powerful.

3. Permeation enhancers

These substances change the skin's ability to act as a barrier to the flow of a desired penetrant, increasing skin permeability. It might be appropriate to group these under the following primary headings:

A. Solvents

These compounds increase penetration possibly by swallowing the polar pathway and/or by fluidizing lipids. Examples include water alcohols – methanol and ethanol; alkyl methyl sulfoxides – dimethyl sulfoxide, alkyl homologs of methyl sulfoxide dimethyl acetamide and dimethyl formamide; pyrrolid- ones- 2 pyrrolidone, N-methyl, 2-purrolidone; laurocapram (Azone), miscellaneous solvents- propylene glycol, glycerol, silicone fluids, isopropyl palmitate.

B. Surfactants

These compounds are proposed to enhance polar pathway transport, especially of hydrophilic

drugs. The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length.

- **Anionic surfactants:** e.g. Dioctylsulpho - succinate, Sodium lauryl sulphate, Decodecyl-methyl sulphoxide etc. Nonionic Surfactants: e.g. Pluronic F127, Pluronic F68, etc.
- **Bile salts:** e.g. Sodium mstaurocholate, Sodium deoxycholate, Sodium tauroglycocholate.
- **Binary system:** These systems apparently open up the heterogeneous multilaminate pathway as well as the continuous pathways.e.g. Propylene glycol-oleic acid and 1, 4-butane diollinoleic acid.

C. Miscellaneous chemicals

These include urea, a hydrating and keratolytic agent, N, N-dimethylm- toluamide, calcium thioglycolate, anticholin- ergic agents.

Some potential permeation enhancers have recently been described but the available data on their effectiveness sparse. These include eucalyptol, di-o- methyl- ßcyclodextrin and soyabean casein.

4. Other excipients

A. Adhesives:- The fastening of all transdermal devices to the skin has so far been done by using a pressure sensitive adhesive which can be positioned on the face of the device and in the back of the device and extending peripherally.

Both adhesive systems should fulfill the following criteria

- Should adhere to the skin aggressively, should be easily removed
- Should not leave an un washable residue on the skin
- Should not irritate or sensitize the skin

The face adhesive system should also fulfill the following criteria

- Physical and chemical compatibility with the drug, excipients and enhancersof the device of which it is a part
- Permeation of drug should not be affected
- The delivery of simple or blended permeation enhancers should not beaffected

B. Backing membrane: -Because they are flexible, backing membranes allow printing, offer a strong attachment to the drug reservoir, and keep the drug from escaping the

dosage form through the top.

These products, such as metallic plastic laminates, plastic backings with absorbent pads and occlusive base plates made of aluminum foil, sticky foam pads made of flexible polyurethane with occlusive bases made of aluminum foil discs, etc., are protected from skin contact by an impermeable substance.

Desirable features for transdermal patches

- Composition relatively invariant in use
- System size reasonable
- Defined site for application
- Application technique highly reproducible
- Delivery is (Typically) zero order
- Delivery is efficient

Factors affecting transdermal drug delivery

Skin condition

The skin's barrier function is maintained by the intact layer, however numerous substances, like acids and alkali, can pass through the skin's barrier cells. Many solvents break down the lipid fraction and create artificial shunts that allow drug molecules to flow through, opening up the intricate, dense structure of the horny layer. Examples of these solvents are methanol and chloroform.

Skin age

It is observed that younger and adult skin is more porous than older skin. However, there isn't a noticeable change. Children's larger surface area per unit body weight has harmful effects. As a result, strong steroids, hexachlorophene, and boric acid have caused serious side effects.

1.2.Types of transdermal patches

There are four major transdermal systems

1. Single-layer Drug-in-Adhesive
2. Multi-layer Drug-in-Adhesive
3. Drug Reservoir-in-Adhesive
4. Drug Matrix-in-Adhesives

1. Interaction studies

For a stable product to be produced, the drug and the excipients need to get along. The drug's stability and bioavailability are impacted by interactions with excipients. Compatibility studies are crucial to the creation of new formulations if the excipients have never been utilized in formulations with the active ingredient. Thermal analysis, Fourier transform infrared spectroscopy (FTIR), ultra violet (UV), and chromatographic techniques are used to conduct interaction studies by evaluating the physicochemical parameters of the materials, such as assay, melting point, wave numbers, and absorption maxima.

2. Thickness of the patch

In order to verify the thickness of the created patch, the thickness of the medication is measured using a digital micrometer at several points along the patch. This yields the average thickness and standard deviation for the same.

3. Weight uniformity

Before testing, the created patches must be dried for four hours at 60°C. A predetermined patch area needs to be divided into multiple sections and then weighed using a digital balance. The individual weights must be used to get the average weight and standard deviation values.

4. Folding endurance

A section of the strip is cut, and it is folded in the same spot repeatedly until it breaks. The value of folding endurance was determined by counting how many times the film could be folded without breaking.

5. Percentage moisture content

The produced patches must be weighed separately and stored at room temperature in a desiccator that contains fused calcium chloride. The films must be reweighed after 24 hours, and the percentage moisture content can be calculated using the formula below.

Percentage moisture content (%) = [Initial weight - Final weight / Final weight] ×100

6. Percentage moisture uptake

To maintain an 84% Rhesus factor (RH), each of the manufactured patches must be weighed separately and stored in a desiccator filled with a saturated potassium chloride solution. The

films must be reweighed after 24 hours, and the method should be used to calculate the percentage of moisture uptake.

Percentage moisture uptake (%) = (Final weight - Initial weight / initial weight) × 100

7. Water vapour permeability (wvp) evaluation

Water vapour permeability can be determined by a natural air circulation oven.

The WVP can be determined by the following formula.

WVP = W/A Where, WVP is expressed in g/m2 per 24 h, W is the amount of vapour permeated through the patch expressed in g/24 h, A is the surface area of the exposure samples expressed in m.

8. Drug content

A predetermined patch area needs to dissolve in a predetermined volume of an appropriate solvent. The solution must then be filtered via a filter media before the drug content is examined using the appropriate technology (UV or HPLC).After that, the mean of three distinct samples is calculated.

9. Content uniformity test

Ten (10) patches were chosen, and each patch's content was established. Transdermal patches pass the content uniformity test if nine out of ten include material that is between 85 and 115% of the prescribed value, and one patch contains content that is not less than 75 to 125% of the stated value. However, an additional twenty patches are tested for drug content if three of the patches have content within the range of 75 to 125%. The transdermal patches pass the test if the range of these 20 patches is between 85 and 115%.

10. Flatness test

From each film, three longitudinal strips were cut at different points, such as the center, the left side, and the right side. Each strip's length was measured, and the percentage constriction—0% constriction being equal to 100%—was used to calculate the length variation resulting from non-uniformity in flatness.

Flatness Constriction (%) = I1 - I2 × 100 I1 Where, I1 = initial length of each strip. I2 = final length of each strip.

11. Percentage elongation break test

The percentage elongation break was determined by noting the length just before the break

point and determined from the formula.

Elongation percentages = L1 - L2 / L2 × 100

Where L1 = final length of each strip

L2 = initial length of each strip.

Peel adhesion properties

Peel adhesion, which refers to the force needed to remove all adhesive covering from test substrate, is crucial for transdermal devices because it dictates the type, quantity, and composition of adhesive that will allow the device to make sufficient contact with the skin. The force needed to pull a single coated tape applied to a substrate at a 180-degree angle is used to test it. For transdermal devices, it is ideal to have no residue on the substrate as this signifies adhesive failure; residue on the substrate, on the other hand, implies cohesive failure. indicating a coating's lack of cohesive strength.

SUMMARY AND CONCLUSION

Six batches of (P1, P2, P3, S4, S5 & S6) Aqueous extract of Azadirachta indica transdermal patches were prepared by solvent casting technique.

The various formulation parameters, Drug-Polymer ratios and permeation enhancers were optimized to get thin, transparent, smooth, stable and high permeable transdermal patches.

The FTIR graphs of drug, excipients and formulations showed that there is no extra peak (or) broadening of peaks were observed and thus it indicates that there is no incompatibility between drug and excipients.

From the optimization, best 2 formulations P2 & S5 were selected based on physico chemical evaluation and in vitro drug diffusion study0.3ml of glycerin was added as plasticizer to produce a flexible patch without having major influence on their diffusion property. If the amount exceeds, the film loses its flexibility and become stiff.

The plasticizer diffuses through the patch and softens the polymer particles. This softening promotes latex coalescence and patch formation.

All the six batches were evaluated for Percentage Moisture uptake, Percentage Moisture content, Thickness, Folding Endurance, Percentage Drug content, Percent Elongation, Tensile strength and Adhesive strength.

The formulations P2 & S5 showed maximum % Moisture uptake, Moisture content, Thickness, folding endurance, % Drug content, Percent elongation, Tensile strength.

No significant difference in drug content was observed between the patches among the six formulations. This indicates the homogenous dispensing of drug during the patch preparation.

The data obtained from in vitro diffusion profile of selected formulations were fitted with various kinetic equations to determine the mechanism of drug diffusion and diffusion rate as indicated by higher correlation coefficients (r^2). The drug diffusion from P2 & S5 follows zero order and non-fickian diffusion.

These findings indicates that the drug diffusion from the P2 & S5 patch was diffusion controlled.

From the results of in vitro diffusion and physicochemical studies, P2 & S5 was concluded as best formulation. Then they were subjected to screening of anti microbial activity.

The anti microbial screening result showed that the P2 was highly inhibit the microbial growth around the patch. So, P2 was selected for further evaluations such as ex vivo and stability studies.

The ex vivo studies results showed 61.01% of drug diffusion at the end of 8 h. It concluded the controlled diffusion property of through the skin.

The stability studies results showed that there is no significant change from its initial nature till the period of three months at 40˚C ±2˚C/75 5% RH.

The present work has achieved the objectives of formulation of transdermal patch of Aqueous extract of Azadirachta indica by using different polymers. The diffusion kinetics confirms that the formulation followed zero order, non-fickian diffusion model.

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