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Herbo-synthetic Transdermal Patch Formulation: A New Approach For Effective Treatment Strategy Of Diabetes Mellitus

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Abstract

Diabetes mellitus (DM)is persistent metabolic disorder in which there is level of blood glucose is increased for prolong period of time. Many medicinal plants and synthetic drugs are used to treat DM. Medicinal plants are known for their antidiabetic activity. Transdermal deliveryof the synthetic drug in combination with the herbswhen administered through transdermal patches shows greater glucose lowering capacity when compared with the synthetic drugs alone with reduced side effects that are associated with the synthetic drugs. Many patients find difficulty in getting injection, or swallowing capsules and tablets. Transdermal patches are better tolerated by the patients with advantage that one can remove the patch when normal glucose level is attained in order to reduce the side effect. These herbo-synthetic patches show great advantage over the conventional dosage form.

Keywords: Diabetes mellitus, transdermal patches, synthetic drugs, medicinal plants, Glucose-level.

Introduction

Diabetes mellitus(DM) describe a metabolic disorder characterized by chronic hyper-glycaemia for prolong period of time with disruption in the metabolism of carbohydrate, protein and fat which may occurs due to the insulin secretion defect, action of insulin or both[1]. Diabetes mellitus cause long-term destruction, inhibition and failure of many organs such as brain, teeth, nerves, eyes, heart and kidneys[2]. If left untreated, it can cause many complications such as heart disease, chronic kidney failure, stroke, and harm to the eyes. Symptoms of DM include frequent urination, increase hunger and increase thirst. DM is due to either enough insulin is not produced by pancreas or the body cells not able to respond properly to insulin produce[3].In the development of diabetes many pathogenetic processes are involved. These include the various processes which demolish the β-cells of pancreas[4]. Due to which enough insulin is not produce. There are

many other factors that result in the insulin action resistance.Various causes of diabetes mellitus is highlighted in figure 1 given below[5]:

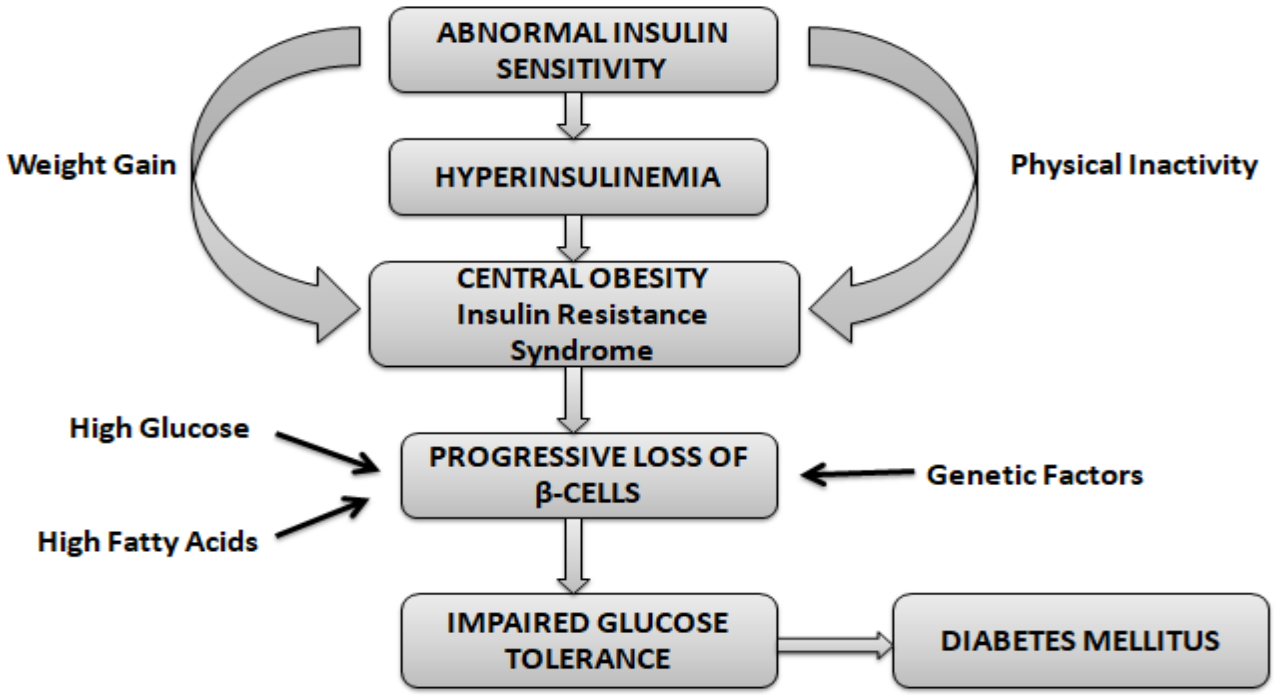

Figure1. Causes of Diabetes Mellitus

WHO Global Report On Diabetes Mellitus

- According to WHO the people that suffer from diabetes has elevated from 108 million in 1980 to 422 million in 2014[6].
- The global ubiquity of DM among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014[7].
- About 1.6 million people were died due to diabetes in 2016[8].
- According to the WHO report almost half of the death ascribable to high blood glucose occurs before the age of 70 years. WHO opinion that in 2016 diabetes was the seventh leading cause of death.
- Diabetes is fast gaining the status of a potential epidemic in India with more than sixty two million diabetic individual currently diagnosed with the disease[9].

Types of diabetes melitus

Diabetes mainly is of three types[3], its classification is given in Figure 2.

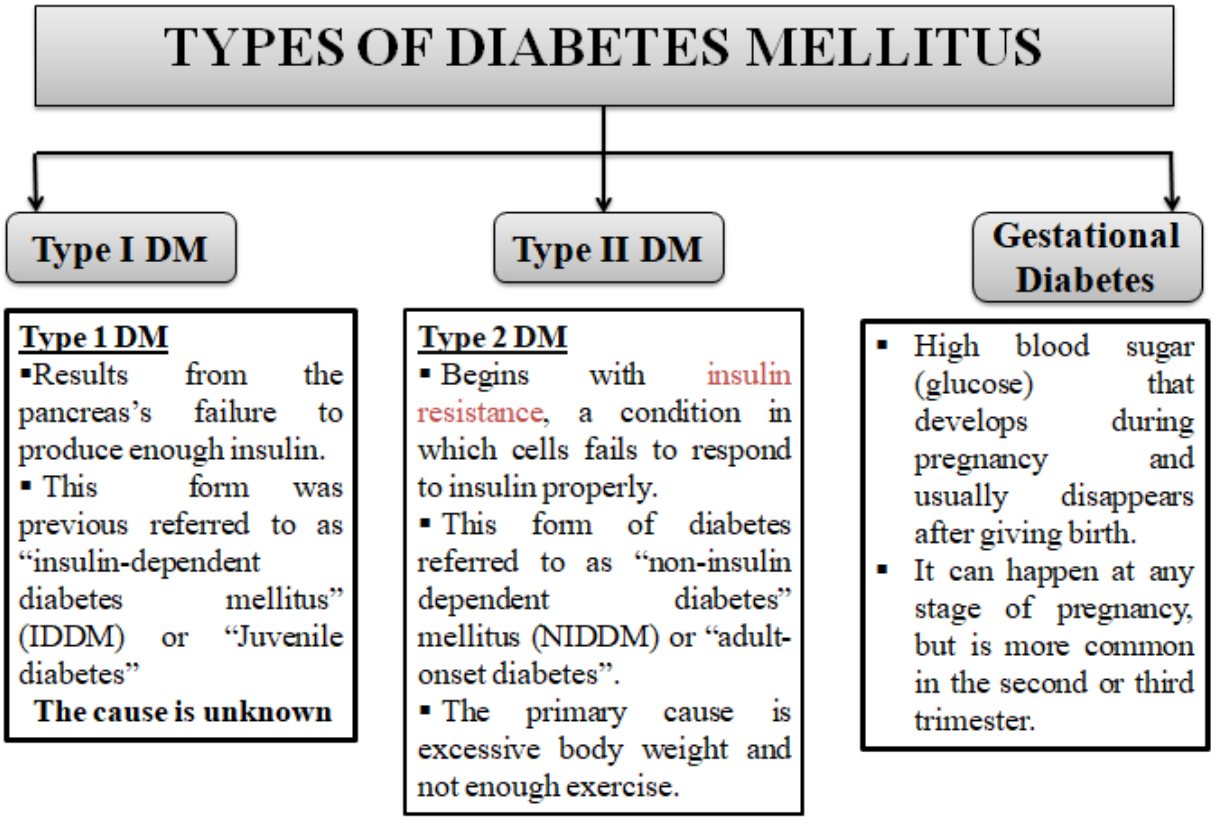

Figure 2.Types of Diabetes Mellitus

Transdermal Patches Containing Medicinal Plant And Synthetic Drug For The Treatment Of Diabetes Mellitus

Delivery of drug by transdermally is the administration of active substance that has therapeutic application through the skin for the systemic effect[10]. Only small number of products that are administered transdermally because in many cases the physical properties of drugs, including polarity and molecular size, have limited its capacity to deliver the particular dug transdermally[11]. Similarly insufficient bioavailability and the dermal irritation have been problematic. A transdermal patch is an adhesive medicated patch that distributes a time-release dose of medication through the skin and then to bloodstream when placed on the skin[12]. Many patients feel difficulty in swallowing tablets, capsules or getting injections. Patches are active for longer periods than tablets and capsules, so patients do not have remembered and follow frequent schedules for taking medication at a specific time. Currently, transdermal patches are used in

several therapeutic areas, including smoking cessation, pain management, hormone replacement, treatment of heart disease, and management of motion sickness[13]. For the treatment of type - IIDM, whendrugs are administered orally it associated with many side effects such as nausea, vomiting, loss of appetite, diarrhoea, stomach upset, constipation, weight gain, liver damage, upper stomach pain[14]. There are many medicinal plants which are known for their antidiabetic activity. If synthetic drugs are fused with the herbal medicinal plants and administered transdermally it reduced major side effects and enhances the antidiabetic activity. Positive interaction between drugs and the herbs lead to enhance the antidiabeticeffect of agents through synergistic or additive actions[15].For the treatment of diabetes mellitus many medicinal plants are used with very less side effects as compare to that of the synthetic drugs[16].

Components of transdermal patches

The main components of transdermal patches are:

Liner **:**During storage it protects the patch, and before use it is removed.

Drug **:**The release liner used in the transdermal patches is in direct contact with theDrug.

Adhesive **:**The various components of the patch are kept together by using adhesive and used to adhere the patch on the skin.

Membrane **:**It manages the liberation of the drug from multi-layer and reservoir patches.

Backing : Patches are protectedfrom outer environment with the help of backing[17].

Preparation of transdermal patches

Matrix-type transdermal patchesare prepared in laboratory by using solvent casting method. A Petri dish is used with a total area of approximately 44.15cm^2. Accurately weighed polymers are dissolved in 10ml of water and methanol (1:1) solution then kept aside to form clear solution. Drug is dissolved in above solution and mixed until clear solution is obtained. Propylene glycol (15% w/w of the total polymer) used as penetration enhancer and polyethylene glycol 400 (30%w/w of total polymer) used as plasticiser. The resultant solution is propelled on the Petri dish which is lubricated with glycerine and dried at room temperature for 24 hours. An inverted funnel is placed over the petri dish to avert the fast evaporation of the solvent. Dried patches are taken out after 24 hours and stored in desiccators[18]. A flow chart of matrix type transdermal patch formulation is shown in Figure 3.

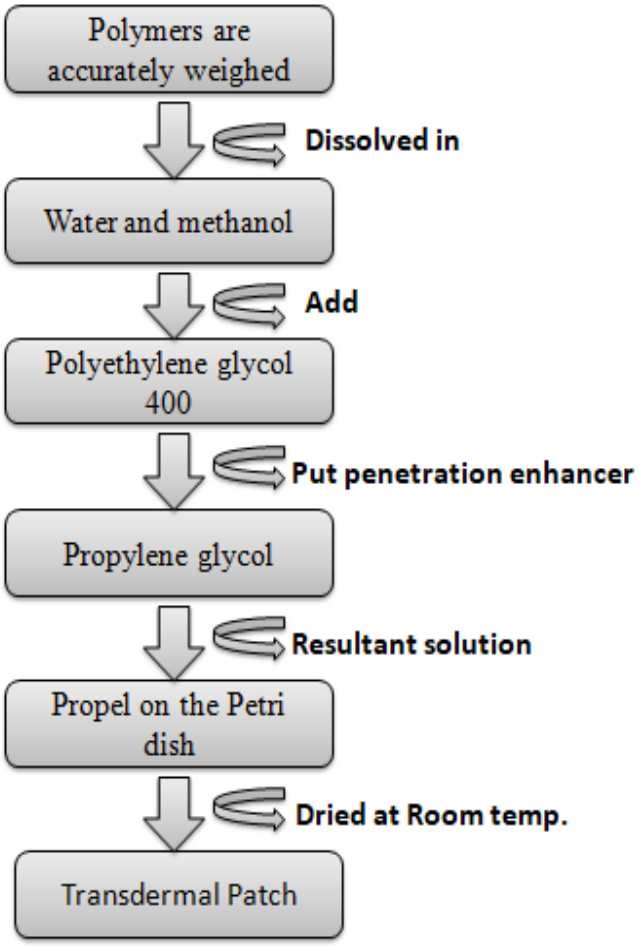

Figure 3. preparation of matrix type transdermal patches

Table1: Common antidiabetic drugs

Compound (Medication)	**Mode of action**	**Appropriate patients**
Sulfonylurea (Daonil®, Glimel, Euglocon®- Glibenclamide or Glybbride® Diabinese=chlorpropamide; Rastinon®=Tolbutamide; Melizide, Glucotrol®,Minidiab®=glipizide; Diamicron®=gliclazide	Increase insulin secretion chronically	Insulinopenic, lean

Meglitinides Repaglinide = Prandin® Nateglinide = Starlix™	Increase insulin secretion acutely	Hyperglycemicpostprandially
α – glucosidase inhibitor Voglibose; Acarbose;=Glucobay®	Decrease postprandial carbohydrate absorption	Hyperglycemicpostprandially
Biguanidines Metformin=Glucophage®; Diabex®; Diaformin	Decrease hepatic glucose production, decrease insulin resistance	Overnight with fasting hyperglycemia
Thiazolidinediones Glitazones (Actos®=pioglitazone	Decrease insulin resistance,decrease hepatic glucose production	Insulin-resistant,overnightdyslipidemic and renal impaired.

Table2: Herbs with antidiabetic activity

Medicinal plant	**Biological source**	**Active constituents**
Aloe vera	Aloe barbadensis	Mannan, galactose-rich polysaccharides and galacturonic acid
Karela	Momordicacharantia	Sterols, glucoside, charantin
Ginger	Zingiberofficinale	Oleoresins, gingerols and other phenolic compounds
Garlic	Allium sativum	Allicin
Gymnema	Gymnemasylvestre	Triterpenoidicsaponins
Astragalus	Radix astragali	Polysaccharides, astragalosides, isoflavones
Scutellaria	Scutellariabaicalesis	Baicalein, baicalin, wogonin, norwogonin

St John's wort	Hypericumperforatum	Naphthodianthrones, hypericin, pseudohypericin
Lycium	Berberislyceum Royal	Polysaccharides & antioxidants

Common drug – Herb Interaction In Diabetes

Aloe vera: Aloeis also used in treatment of diabetes mellitus. In pancreatic beta cells it suppress ATP sensitive potassium channel, exert its antidiabetic activity when interact with the glibenclamide, resulting depolarisation and cause release of insulin[20]. Combination of these two shows additive effect and produced greater hypoglycaemic effect[21].

Karela: Karela is used in combination with other antidiabetic drugs such as metformin, glibenclamide, glymidine in NIDDM patients to produce antidiabetic effect[22]. It is found that about 400mg of chloroform or benzene extract was united with 50% full dose of glibenclamideor metformin shows greater antidiabetic effect that estimated in one clinical trial[23].Karela extract and metformin shows greater hypoglycaemic effect than alone in rat model of diabetes[24].

Ginger: Combination of glibenclamide (5mg/kg) with extract of ginger (25 or 50mg/kg) can reduced the non-fasting level of blood glucose by 26 and 25% respectively, compared to 7.9% reduction when glibenclamide used alone[25]. It is more effective than glibenclamide alone when ginger given with glibenclamidefor the treatment of STZ induced diabetic model and also reduces the side effects associated with the glibenclamide[26]. Ginger shows protective effect of renal when used with metformin[27].

Garlic : Metformin combination with the garlic can lower the level of blood glucose or have greater antidiabetic effect[28].Garlic composed of a large number of sulfur compounds, with suspected bioactive compounds called allylthiosulfinates (mainly allicin)[29].

St. John's wort : It has also reported that it has antidiabetic activity as well as it is known for antidepressant action[30]. When it gives in combination with the metformin it show additive effect and have greater antidiabetic activity[31].

Scutellaria: Several chemical compoundshave been isolated from the root of scutellariaincludingbaicalein, baicalin, wogonin, norwogonin,oroxylin A and β-sitosterol[32].The combined administration of ethanolic extract of scutellaria (400mg/kg) and metformin

(500mg/kg) for 30 days can reduced the level of blood - glucose when investigatedin Streptozotocin induced rat model.

Andrographispaniculata:This herb s commonly used to treat diabetes[33]. It inhibits CYP2C19 activity[34] for which the antidiabetic drugs such as Glipizide, glimepiride, glibenclamide, pioglitazone that subsequent enhanced glucose lowering effect. But there are no studies that examined the interaction between the antidiabetic drugs and *Andrographispaniculata*.

Lycium:Lycium has antidiabetic effect[35]. Its hypoglycaemic effect is due to antioxidants and bioactive polysaccharides. The combination of the Lycium with the glibenclamide shows the additive or positive effect, have greater glucose lowering effect with reduced side effects[36].

Table3: Herb–antidiabetic drug co-administration studies

Herb	**Co-administered anti-diabetic drug**	**Experimental/clinical study**	**Observation**
Aloe vera	Glibenclamide	clinical	Additive effect on blood glucose lowering[21].
Andrographispaniculata	NA	Experimental	Hypoglyceamic effect inhibits CYP2C19 activity[37]
Karela	Metformin	Clinical	Significant decrease in serum glucose was observed in combination of fruit juice extract at half normal dose of metformin[23].
Ginger	Glibenclamide	Experimental	It reduced the blood glucose level[25].
Lycium	Antidiabetics	Experimental	Significant reduction in glucose[35].
Garlic	Metformin	Experimental	Resulting in blood glucose level[38].
St.Johnwort	Metformin	Clinical	Improve the glucose tolerance by enhancing insulin secretion

			independently of insulin sensitivity in male subject taking metformin[38].
Scutellaria	Metformin	Experimental	Herb enhance the antidiabetic action of metformin. Significant elevation of plasma and pancreatic level and reduction of plasma and hepatic level of triglycerides and cholesterol[39].

Conclusion

It has been concluded that there are many medicinal plants that have antidiabetic activity. These plants are known for their very less side effect as compared to that of synthetic drugs. There are many studies that show the additive or synergistic effect of herbs with the drugs. When one can use the herbal drug with the other synthetic drugs there is decrease in the dose of synthetic drugs and has more effectiveness.

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