

Bridging Between Disease, Prevalence and Treatment of Diabetes Mellitus : A Review

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Abstract: Diabetes mellitus (DM) is one of the oldest diseases known to man. DM is a chronic metabolic disorder resulting from a reduced insulin secretion by the pancreas or insulin action in the body or both. Currently 200 million people worldwide are found to be affected with DM and it is estimated and expected to reach 300 million by 2025. People can live normal with a healthy live by combining the elements of a balanced and nutritious diet, regular exercise or physical activity and proper medication. A regular blood glucose testing at intervals will be a guide to control the disease. Despite the publication of numerous original and review articles on the subject and availability of many natural as well as synthetic marketed products the effective management and treatment is not understood. This article highlights an overview of the historical background of the diabetes, classification (i.e., Type-I, Type-II, gestational, genetic defects of the β -cell), pathological changes and complications. It is briefed on treatment and management of the diabetes and the novel drug delivery systems such as nanoparticles, liposomes, aquasomes, emulsosomes, ethosomes, transdermals, microspheres, and implant in therapy. Thus, a better understanding concerning the DM and novel approaches in formulation technology and therapy could guide the formulation scientists and clinicians towards successful management of DM.

Keywords: diabetes mellitus, treatments, drug, novel approaches, formulation.

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder of impaired metabolism of carbohydrates, fats, and proteins, characterised by hyperglycaemia resulting from decreased utilisation of carbohydrate and excessive glycogenolysis and gluconeogenesis from amino acids and fatty acids⁽¹⁾. Diabetes is one of the first diseases described with an Egyptian manuscript mentioning "too great emptying of the urine"⁽²⁻³⁾. Indian physicians around the same time identified the disease and classified it as "Madhumeha" or "Honey urine", noting the urine would attract ants. The term "diabetes" or "to pass through" was first used in 230 BCE by the Greek Apollonius of Memphis. Galen named the disease "diarrhoea of the urine" (diarrhoea urinosa)⁽⁴⁾. DM resulting from reduced insulin secretion from pancreas, insulin action in the body or both. Diabetes may present with characteristic symptoms such as thirst, polyurea, blurring of vision, and weight loss. In its most severe forms, ketoacidosis or a non ketotic hyperosmolar state may develop and lead to stupor, coma, in absence of effective treatment, death⁽⁵⁻⁷⁾. The long-term effects of DM include progressive development of the specific complications of retinopathy with potential blindness, nephropathy lead to renal failure, neuropathy with risk of foot ulcers, amputation, charcot joints, autonomic dysfunctions, sexual dysfunctions⁽⁸⁾. There are several natural as well as synthetic drugs like insulin, biguanides, sulfonyl ureas, thiazolidinediones,

meglitinides etc. are used in the treatment of diabetes⁽⁹⁻¹⁰⁾. Nanoparticles, liposomes, aquasomes, emulsosomes, ethosomes, controlled release, bio adhesive, are novel approaches requisite in the formulation for better delivery of drugs⁽¹¹⁾.

Prevalence

The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. There are 382 million people living with diabetes worldwide. The prevalence of diabetes is higher in men than women, but there are more women with diabetes than men. The worldwide prevalence of diabetes in adults (aged 20-79 years) was estimated to be 135, 285 million in 1995 and 2010 respectively and is expected 300 million in 2025 and 439 million in 2030. Statistics showed significant increase (155 million) of diabetes in adults from 1995 to 2010. By 2035, 592 million people or 1 in 10 people will have diabetes and 316 million people are currently at high risk of developing type 2 diabetes, with the number expected to increase to almost 500 million within a generation. It is higher in developed than in developing countries. By the year 2025, more than 75% of people with diabetes will reside in developing countries, as compared with 62% in 1995. In 2012 it resulted in 1.5 million deaths worldwide making it the 8th leading cause of death and more than 80% of diabetic deaths occurring in low and middle-income countries. More than 21 million live births were affected by diabetes during pregnancy and > 79,000 children developed type 1 diabetes in 2013. Europe has the highest prevalence of type 1 diabetes in children but in South-East Asia, almost half of people with diabetes are undiagnosed. 11% of people with diabetes live in Middle East and North Africa where as it was 6% in Africa but in Africa, 76% of deaths due to diabetes are in people under the age of 60. North America and the Caribbean spent more on healthcare for diabetes than in any other region (Figure 1)⁽¹²⁻¹⁷⁾.

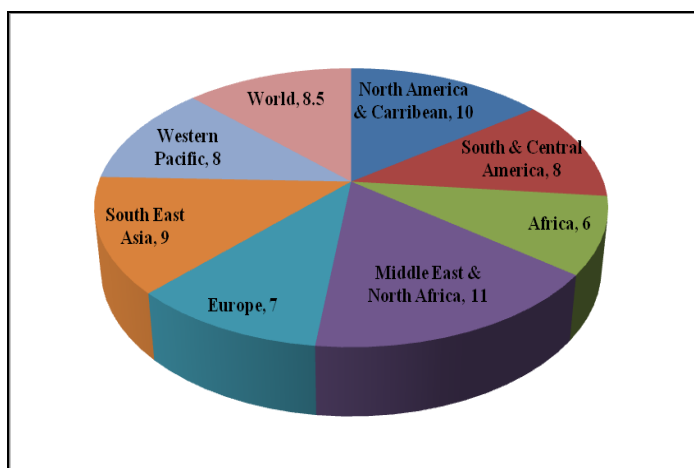


Figure1: Prevalence (%) of diabetes in adults, 2013

According to the International Diabetes Federation survey in the year of 2013, nearly 98.4 million people with diabetes (at 20-79 years) live in China, is the top most country and India is the second i.e., nearly 65.1 million. **Table 1** presents survey of the year 2013 on diabetes affected top 10 countries and their number of diabetic people at age group of 20-79.

Table 1: Top ten countries with diabetes and their number of people at age group of 20-79. Source: International Diabetes Federation Diabetes Atlas, Sixth Edition, 2013.

Sr. no.	Country/Territory	Number (million)
1.	China	98.4
2.	India	65.1
3.	United States of America	24.4
4.	Brazil	11.9
5.	Russian Federation	10.9
6.	Mexico	8.7
7.	Indonesia	8.5
8.	Germany	7.6
9.	Egypt	7.5
10.	Japan	7.2

Classification of Dm

DM is classified into four broad categories: type 1, type 2, gestational diabetes and other specific types⁽¹⁸⁾. The "other specific types" are a collection of a few dozen individual causes.

Type 1 DM is characterized by loss of the insulin producing beta cells of the islets of langerhans in the pancreas, leading to insulin deficiency. The majority of type 1 diabetes is of the immune-mediated nature, in which a T- cell- mediated autoimmune attack leads to the loss of beta cells and thus insulin. Traditionally it is termed as juvenile diabetes because a majority of these diabetes cases were in children⁽¹⁹⁻²¹⁾.

Type 2 DM is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion. In the early stages of type 2, the predominant abnormality reduced insulin sensitivity. At this stage, hyperglycaemia can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce glucose production by the liver⁽²²⁻²⁴⁾. Type 2 diabetes is due primarily to genetics and lifestyle factors including obesity, lack of physical activity, poor diet, stress and urbanization. A lack of exercise is believed to cause 7% of cases⁽²⁵⁻²⁶⁾.

Gestational DM (GDM) involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2-10% of all pregnancies and may improve or disappear after delivery. Management of GDM may include dietary changes, blood glucose monitoring, and in some cases insulin may be required⁽²⁷⁾.

Prediabetes occurs when a person's blood glucose levels are higher than normal but not high enough for a diagnosis of type 2 DM. Latent autoimmune diabetes of adults (LADA) is a condition in which type 1 DM develops in adults and initially misdiagnosed as having type 2 DM, based on age rather than etiology⁽²⁸⁾. Comprehensive lists of causes of DM with examples are given in the Table 2.

Table 2: Comprehensive list of other causes of diabetes⁽²⁹⁻³³⁾.

Causes	Examples
Genetic defects of β -cell function	Maturity onset diabetes of the young Mitochondrial DNA mutations
Genetic defects in insulin processing or insulin action	Defects in proinsulin conversion, Insulin gene mutation Insulin receptor mutation
Exocrine pancreatic defects	Chronic pancreatitis, Pancreatectomy, Pancreatic neoplasia, Cystic fibrosis, Hemochromatosis, Fibrocalculous pancreatopathy
Endocrinopathies	Growth hormone excess, Cushing syndrome, Hyperthyroidism, Pheochromocytoma, Glucagonoma
Infections	Cytomegalovirus infections, Coxsackievirus B
Drugs mediated	Glucocorticoids, Thyroid hormone, β -adrenergic agonists, Statins

Symptoms and Complications

Symptoms are similar in both types of diabetes but they vary in their intensity. Symptoms develop more rapidly in type 1 diabetes and more typical. The symptoms of diabetes include frequent urination, extreme thirst and/or hunger, weight loss, fatigue, numbness and increased infections. People with diabetes have an increased risk of developing a number of serious health problems. Poor control of diabetes can lead to an increased risk of heart disease, high blood pressure, stroke, nerve disease, kidney and bladder failure, gum disease, blindness, foot and leg infections, sexual dysfunctions, pregnancy complications. Uncontrolled diabetes can lead to biochemical imbalance that can cause life-threatening events, such as diabetes ketoacidosis and hyperosmolar coma⁽³⁴⁻³⁵⁾.

Diabetic nephropathy

Diabetic nephropathy affects 20-30% of patients with DM. It is a progressive condition culminating into a kidney failure. It has been classically defined by the presence of proteinuria greater than 0.5g/24 h. This data suggest that inhibition of Aldose Reductase in kidney contributes to the protective effect on diabetic kidney. Maintaining near normal levels of blood glucose and blood pressure can greatly reduce the risk of kidney disease⁽³⁶⁻³⁸⁾.

Diabetic neuropathy

Neuropathy is a common complication of both type 1 and type 2 DM. These are characterised by diffuse or focal damage to peripheral somatic or autonomic nerve fibres resulting from DM. Diabetes can cause damage to the nerves throughout the body when blood glucose and blood pressure are too high. This leads to problems with digestion, erectile dysfunction. Among the most commonly affected areas are the extremities, in particular the feet. Nerve damage in these areas is called peripheral neuropathy, and can lead to pain, tingling, and loss of feeling ⁽³⁹⁻⁴⁰⁾.

Diabetic cataract

Cataract is a condition where the crystalline lens of the eye loses its transparency. DM has been associated with an increase in cataract among adults ⁽⁴¹⁾. It is mainly caused by swelling of crystalline lens due to osmotic changes caused by increased sorbitol concentration ⁽⁴²⁾.

Diabetic retinopathy

Diabetic retinopathy (DR) is the most common ocular complication in DM and is an important cause of preventable blindness. DR is broadly classified as non proliferative DR involving intraretinal micro vascular changes and proliferative DR involving the formation of new vessels or fibrous tissue or both on the retina ⁽⁴³⁾. High levels of blood glucose, together with high blood pressure and high cholesterol, are the main causes of retinopathy. It can be managed through regular eye checks and keeping glucose and lipid levels at or close to normal.

Pregnancy complications

High blood glucose during pregnancy can lead to the foetus putting on excess weight. This can lead to problems in delivery, trauma to the child and mother, and a sudden drop in blood glucose for the child after birth. Children who are exposed for a long time to high blood glucose in the womb are at higher risk of developing diabetes in the future ⁽⁴¹⁻⁴³⁾.

Diabetes (both type 1 and type 2) can be diagnosed or detected based on presence of symptoms, blood sugar estimation, oral glucose tolerance test.

1. A1C assay $\geq 6.5\%$. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay. Or,
2. FPG ≥ 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h. Or,
3. 2-h plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. Or,
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dl (11.1 mmol/l). However it should be noted that in the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing ^(7, 44).

Treatment of Diabetes

New treatment plans for diabetes today have certain things in common that apply to both type 1 and type 2 diabetes. People can live normal, healthy lives by combining the elements of balanced diet, regular exercise and proper medicine ⁽⁴⁵⁻⁴⁹⁾. Oral hypoglycaemics are classified into sulfonylureas, biguanides, α -glucosidase inhibitors, meglitinides and thiazolidinediones. Table 3 presents the category, brand name, mechanism of action and side effects of the insulin and oral hypoglycaemics.

Table 3: Drugs used in the treatment of DM

Category	Drug name	Brand name	Mechanism of action	Side effects	References
Insulin	Insulin glulisine Insulin lispro Insulin NPH Insulin regular Insulin galrgine Insulin detemar Insulin aspart	Apidra Humalog Novolin N Novolin R Lantus Levemar Novolog	Insulin lowers blood glucose by peripheral glucose uptake and by inhibiting hepatic glucose production	Hyperglycaemia Oedema Weight gain	50-52

Biguanides	Metformin	Fortamet Glucophage	Improves the glucose tolerance by lowering both basal and postprandial plasma glucose	Lactic acidosis Megaloblastic anaemia Diarrhoea Vomiting Dyspepsia Flatulence	53-56
Di-peptidyl peptidase-4 inhibitors (DPP-4)	Sitagliptin Saxagliptin Linagliptin	Januvia Onglyza Tadjenta	It enhances the activity of active GLP-1, thus increasing glucose-dependent insulin secretion and decreasing the level of hepatic glucose production	Acute pancreatitis Diarrhoea Vomiting Nausea	57-59
Sulfonyl ureas	First generation drugs: Tolbutamide Acetohexamide Tolazamide Second generation drugs: Glimepiride Glipizide Gliquidone Glibenclamide	Orinase Dymelor Tolinase Amryl Glucotrol Glurenorm Disbeta	They are insulin secretagogues and Stimulating the insulin release by inhibiting the K_{ATP} channels of the pancreatic β cells	Hypoglycaemia Weight gain	60-62
Thiazolidinediones	Rosiglitazone Pioglitazone Troglitazone	Avandia Actos Rezulin	They affecting the peroxysome proliferators activated receptor <u>PPAR-γ</u> , by acting as agonist these receptors, they decreases insulin resistance in adipose tissue, skeletal muscle and the liver ⁽⁶⁴⁻⁶⁵⁾ .	Hepatic failure Heart failure Anaemia Bone loss	63-65
Meglitinides	Repaglinide Nateglinide	Prandin Starlix	By closing the potassium channels of the pancreatic beta cells, they open the calcium channels, thereby enhancing insulin secretion.	Weight gain Hypoglycaemia	66-68
Alpha-glucosidase inhibitors	Miglitol Acarbose	Glyset Precose	Slows the digestion of starch in the small intestine so that glucose from a starch enters more slowly into the blood stream	Diarrhoea Vomiting	69-75
Injectable Amylin analogues	Amylin analogue	Pramlintide	Slows gastric emptying and suppress glucagon	Nausea	76

Several drug combinations have become available to treat type 2 diabetes. These drugs would have been given together so combining them into one tablet or capsule may help encourage patient compliance. Combination therapy using agents with complementary but different mechanism of action that address different path physiologic defects of type 2 diabetes may improve glycemic control to a greater extent than monotherapy. Combination therapy may also allow the use of lower doses of concomitant anti hyperglycaemic agents, which may minimize unwanted side effects. Combination drug therapy for the treatment of DM was described in Table 4.

Table 4: Combination drug therapy for the treatment of DM ⁽⁷⁷⁻⁷⁹⁾

Sl. No.	Combination of drugs	Significance
1.	Insulin and metformin	Improves FPG and reduces insulin dosage (25-30%)
2.	Pioglitazone/ rosiglitazone and sulfonyl urea	Unable to tolerate metformin or combination of metformin
3.	Glyburide and metformin	Better glyceemic control
4.	Metformin and pioglitazone	Preferred diabetes with obese patient
5.	Glipizide and metformin	Better glyceemic control
6.	Metformin and repaglinide	More effective or when metformin alone is inadequate
7.	Metformin and rosiglitazone	Preferred diabetes with obese patient
8.	Glimepiride and pioglitazone	Better glyceemic control
9.	Glimepiride and rosiglitazone	Better glyceemic control

Natural anti diabetes

Plants are a potential source of anti-diabetic drugs. The ethno botanical information reports that about 800 plants may possess anti-diabetic potential ⁽⁸⁰⁻⁸²⁾. A wide array of plant derived active principles representing numerous chemical compounds like flavonoids, alkaloids, glycosides, polysaccharides, peptidoglycons, hypoglycons, guanidines, steroids, carbohydrates, glycopeptides, terpenoids and amino acids has demonstrated activity consistent with their possible use in the treatment of non-insulin dependent DM (NIDDM) ^(83.-87). The mechanisms of action include promoting regeneration of β cells of islets of langerhans in the pancreas, enhancement of insulin release and activity on the cells, decrease peripheral glucose uptake at the duodenal cellular level and other aspects of small intestine. Restriction of the rise in blood glucose levels caused by pituitary hormones responsible for inhibiting peripheral utilization of glucose as well as glycogenolysis, and the presence of high level of fibre in plants which interferes with carbohydrate absorption ⁽⁸⁸⁻⁹¹⁾. The active compounds present in the plant with confirmed anti diabetic properties are given in the Table 5.

Table 5: Examples of plants with confirmed anti diabetic properties ⁽⁹²⁻⁹⁸⁾:

Botanical name	Used part	Active compounds
Gallege officinalis	Leaves, seeds	Galegine
Syzygian cumin	Leaves, seeds and flowers	Mycaminose
Boubinia forficata	Leaves, bark and flowers	Kaempferol-3-neo hesperidoside
Bidense pilosa	Whole plant	Polyacetylenic glycosides
Swertia punicea	Whole plant	Bellidifolin
Capparis moon	Fruits	Gallotannins
Salacia reticulata	Root, stem	Slacilol, kotalonolol, De-O-sulfared kotalonol, ponkolonol, salaprinol
Morus alba	Leaves	Chalcomoracin, moracin C, maoracin D, moracin N
Acacia pennata	Shoot tips	Polyphenols, caffiec acid
Solanum xanthocarpum	Fruits	Polyphenols, caffiec acid
Salacia oblonga	Root, stem, leaves	Salacinol, kotalanol, mangiferin.
Ruta graveolens	Leaves	Rutin
Carissa carandas	Fruits	Gallic acid, flavonoids
Artemisia dracunculus L.	Whole plant	Davidigenin, sakuranetin, 2',4'-dihydroxy-4-methoxydihydrochalcone, 4,5-di-O-caffeoylquinic acid, 5-O-caffeoylquinic acid, 6-demethoxycapillarisin
Ocimum santum	Leaves	Poly phenols, caffiec acid, p-coumaric acid
Eluetherine Americana	Bulb	Eluthoraside A

Aquilaria sinensis	Leaves	Mangiferin, iriflophenon2-O- α -L-ramnopyranoside, iriflophenon3-C- β -D-glucoside
Macaranga tanarius	Seeds	Ellagitannins
Solaceae oblonga	Root, stem, leaves	Salacinol, kotalanol, mangiferin.
Panax Japonicus	Root	Polyacetylenes, phenolics compounds, one susequiterpinoid, sterol glycoside
Curcuma longa	Rhizome	Curcumin, ar-turminone,
Aronia melanocarpa	Fruits	Anthocyanins

Novel Approaches in Formulation of Anti Diabetics

Various novel approaches have been demonstrated to formulate the anti diabetic drugs for their better absorption, bioavailability and therapeutic efficacy. Some of the novel approaches or techniques for formulation of medicines for better delivery of drugs are given below.

1. Delivery of Insulin

a. Nano carriers

These are carriers with a particle size of less than 1000 nm. It received more attention recently due to their submicron size and their large specific surface area, both of which favour their absorption compared to larger carriers. Category of nano carriers are presented in the Figure 2.

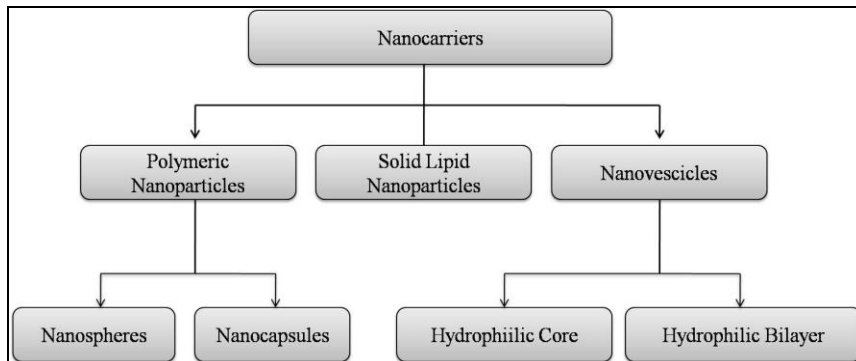


Figure 2: Classification of nano carriers

Polymeric nanoparticles developed from biocompatible and biodegradable polymers are good candidates for insulin delivery. There are two types of polymeric nanoparticles: the matrix particles termed 'nanospheres' and the reservoir-type named 'nanocapsules'⁽⁹⁹⁾. Insulin loaded liposomes containing sodium glycocholate elicited higher bioavailability of approximately 8.5% and 11.0% in non-diabetic and diabetic rats, respectively⁽¹⁰⁰⁾. A hepatic directed vesicle insulin system (HDV-I) was developed by Diasome Pharmaceuticals. The oral administration of insulin-loaded vesicles to diabetic mice resulted in the reduction of blood glucose levels 25% of the initial glucose level which was maintained at this level for an additional 18.5 hours⁽¹⁰¹⁾. Insulin was solubilised into mixed reverse micelles of sodium cholate and soybean phosphatidylcholine and transformed into SLN using a novel reverse micelle-double emulsion technique⁽¹⁰²⁾.

b. Lipid-based systems

Lipid-based delivery systems (LDS) range from simple oil solutions to complex mixtures of oils, surfactants, cosurfactants and cosolvents. The bioavailability of several peptides was improved when incorporated into LDS e.g., cyclosporine (Neoral®). Categories of lipid based systems are present in the Figure 3.

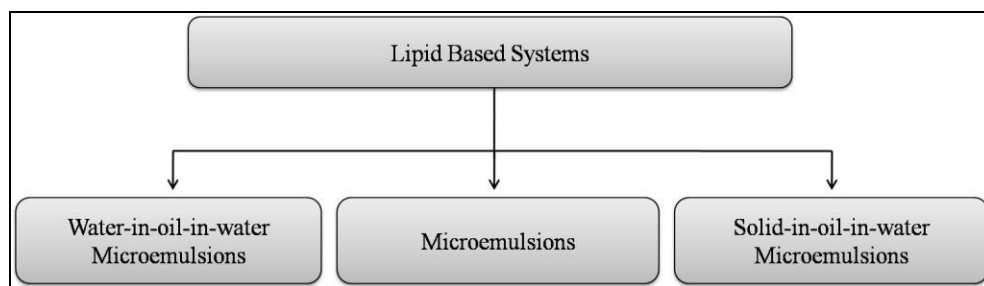


Figure 3: Categories of lipid based systems

A water-in-oil-in-water (W/O/W) emulsion has been proposed to protect peptides against proteolysis and enhance their absorption. Multiple emulsions containing unsaturated fatty acids (oleic acid, linoleic acid and linolenic acid) have been reported to enhance the ileac and colonic absorption of insulin without tissue damage⁽¹⁰³⁾. Microemulsions are clear, stable, isotropic mixtures of oil, water and surfactant, frequently in combination with a cosurfactant⁽¹⁰⁴⁾. Insulin loaded microemulsions were developed using didodecyl dimethylammonium bromide as the surfactant, propylene glycol as the cosurfactant, triacetin as the oil phase and insulin solution as the aqueous phase. These micro emulsions displayed a 10-fold enhancement in bioavailability compared with a plain insulin solution administered orally to healthy rats⁽¹⁰⁵⁾. S/O/W emulsions were also developed for the delivery of insulin whereby insulin was converted into a lipophilic complex by coating with surfactant molecules and dispersed in an oil phase of oil in a water emulsion to form the S/O/W emulsion⁽¹⁰⁶⁾.

Future trends of insulin delivery

Newer injectable insulins

Newer insulins that are promising include long acting basal insulin analogue called insulin degludec and ultra fast acting insulin, human insulin Linjeta™ (formally called VIAject)⁽¹⁰⁷⁾. Insulin degludec, a novel ultra-long acting basal insulin, is almost identical to human insulin in structure and this insulin forms soluble multihexamers after subcutaneous injection, resulting in an ultra-long action profile with half life more than 24 hours⁽¹⁰⁸⁾. Insulin degludec is not yet approved by Food and Drug Administration. VIAject is recombinant human insulin with ultra fast onset of action. Pharmacodynamic and pharmacokinetic studies have shown the onset of action of VIAject is faster than that of human soluble insulin and insulin lispro⁽¹⁰⁹⁾.

Artificial pancreas

Introduction of continuous glucose sensors has led to development of the artificial pancreas, which made improved care possible. Closed-loop insulin delivery, also referred to as the artificial pancreas, is an emerging therapeutic approach. In this closed-loop, blood glucose control is achieved using an algorithm, wireless communication of a continuous glucose monitor linked to insulin infusion pump that facilitates automated data transfer and delivers insulin, without the need for human intervention⁽¹¹⁰⁾.

Buccal delivery of insulin

Insulin delivered by buccal delivery system is through an aerosol spray into the oral cavity and hence, differs from inhalers. The insulin is absorbed through the inside of the cheeks and in the back of the mouth instead of the lungs. Nanoparticles are pelleted to impart three dimensional structural conformity and coherence thereby facilitating of buccal delivery of insulin⁽¹¹¹⁾.

Inhaled insulin

Insulin inhalers would work like asthma inhalers. The products fall into two main groups: the dry powder formulations and solution, which are delivered through different patented inhaler systems. Exubera® containing rapid-acting insulin in powder form, has been studied extensively in patients with type 1 and type 2 diabetes mellitus. Exubera® was available for a short time (August 2006 to October 2007). In October 2007, Pfizer took off Exubera off the market as the drug failed to gain market acceptance⁽¹¹²⁾.

2. Delivery of other anti diabetes

Control release tablets

Sustained drug delivery systems are designed to achieve a continuous delivery of drugs at predictable and reproducible kinetics over an extended period of time in the circulation. The potential advantage of this concept include minimization of drug related side effects due to controlled therapeutic blood levels instead of oscillating blood levels, improved patient compliance due to reduced frequency of dosing and the reduction of the total dose of drug administered⁽¹¹³⁻¹¹⁴⁾.

Bio adhesive tablets

Drug delivery systems are designed for prolonged retention on the mucosa to facilitate drug absorption over a prolonged period of time by interacting with mucin⁽¹¹⁵⁾. Bio adhesive delivery of metformin using prosopis gum with anti diabetic potential indicates that in combination with metformin in a bio adhesive form, the glucose lowering effect was found to be synergistic. The areas under the effect vs. time curves (AUECs) were much higher when combined in a bio adhesive form than with the drug alone⁽¹¹⁶⁾.

Floating tablets

Floating drug delivery systems are of particular interest for drugs that have narrow absorption window in stomach, unstable in the intestinal environment, and exhibit low solubility at high pH values. Floating systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach. Floating tablets of rosiglitazone maleate was developed using gas forming agents, like sodium bicarbonate, tartaric acid and natural gums like xanthane gum and gaur gum and shows better solubility in the stomach⁽¹¹⁷⁾.

Matrix tablets

The most convenient way to achieve controlled release of active agent involves physical blending of drug with polymer matrix, followed by direct compression, compression moulding, injection moulding, extrusion, or solvent casting which results either in monolithic device or in swellable hydrogel matrix⁽¹¹⁸⁻¹²¹⁾. Glipizide, when it is formulated as matrix tablet, it appears to be the most effective insulin secretagogue both in first phase insulin secretion and in sustained stimulatory response during long term administration⁽¹²²⁾.

Nanoparticles

Nanoparticles (NPs) can be used as a multiparticulate delivery system to obtain prolonged or controlled drug delivery, as well as to improve bioavailability and drug stability⁽¹²³⁾. Other advantages of NPs include limitation of fluctuations within the therapeutic range, a reduction in side effects, decreased dosing frequency, and improved patient compliance⁽¹²⁴⁻¹²⁵⁾. The gastrointestinal absorption rate of glipizide increased with nanoparticles⁽¹²⁶⁾.

Cyclodextrins/Complexation

Cyclodextrins (CDs) are non-toxic cyclic oligosaccharides containing at least 6 D-(+)-glucopyranose units attached by α -(1, 4) glucosides bonds. As a result of their molecular structure, with hydrophilic exterior surface and hydrophobic cavity interior, cyclodextrins possess a unique ability to form inclusion complexes with many drugs and increases their solubility⁽¹²⁷⁻¹²⁸⁾. Development of β -cyclodextrin based sustained release micro particles for oral insulin delivery, shows better insulin solubility than other formulations⁽¹²⁹⁾.

Microspheres

The floating microspheres have been utilized to obtain prolonged and uniform release in the stomach for development of a once daily formulation. The major advantage of the preparation technique includes short processing time, the lack of exposure of the ingredients to high temperature, and high encapsulation efficiencies. Metformin hydrochloride floating microspheres were prepared by non aqueous emulsification solvent evaporation technique using ethyl cellulose as the rate controlling polymer⁽¹³⁰⁾.

Bilayer tablets

The main object to produce a bilayer tablet with two different release profiles with glibenclamide as immediate release layer and metformin hydrochloride as a sustain release layer to provide a desired pharmacokinetic and therapeutic action. Glibenclamide is not capable of acting on insulin resistance, and metformin hydrochloride is not able to stimulate insulin secretion. Rational for combination of glibenclamide with metformin hydrochloride suggest the use of combined formulation of medicaments capable of finding a remedy for both the deficiency in insulin secretion and the insulin resistance conscription⁽¹³¹⁾.

Drug loaded pellets

Controlled drug delivery systems significantly enhances therapeutic efficacy of drugs. Drug release retarding polymers are the performers in such designed systems. A wide range of polymers like natural, semi-synthetic and synthetic from various origins are investigated as drug retarding polymeric materials. Gliclazide loaded pellets developed by green synthesis technique where in gum kondagogu is used as natural drug trending polymer⁽¹³²⁻¹³⁴⁾.

Liquisolid compacts

A liquisolid system is the one of the novel technique to enhance the dissolution rate of poorly water soluble drug such as nateglinide. Liquisolid system refers to formulations formed by conversion of liquid drugs, drug suspensions or solutions in non volatile solvents into dry, non adherent, free flowing and compressible powder mixture⁽¹³⁵⁻¹³⁶⁾. The liquid solid compacts of glibenclamide have achieved the fast dissolving effect and enhanced bioavailability⁽¹³⁷⁾.

Micro encapsulated systems

An advanced micro encapsulated system is a platform for optimized oral delivery of anti diabetic drug-bile acid derivative formulations as they have good and uniform structural properties⁽¹³⁷⁾. Each individual microcapsule offer greater uniformity and reproducibility and having greater safety factor in case of a burst or defective individual in subdivided dosage forms. Micro encapsulation of gliclazide-cholic acid derivative mixture was carried out using Buchi-based micro encapsulating system by using sodium alginate polymer and shows the enhanced bioavailability⁽¹³⁹⁻¹⁴⁰⁾.

Transdermal drug delivery systems

Transdermal drug delivery systems are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. Advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug⁽¹⁴¹⁾. A novel matrix controlled transdermal systems of anti diabetic drug glimepiride were prepared using natural polymer chitosan. This study demonstrated that this novel matrix controlled transdermal delivery system exhibited better control of diabetes than conventional oral route⁽¹⁴²⁾.

Ethosomes

Ethosomes has become new liposome carriers with high deformity and high entrapment efficiency and good transdermal permeation rate. The ethosomes consists of phospholipids, isopropyl alcohol, propylene glycol and cholesterol. The efficacy of ethosomes contributes to the synergistic effect of phospholipids and propylene glycol⁽¹⁴³⁾. An ethosomal system successfully deliver repaglinide transdermally and sustain its effect and reduce its dosing frequency⁽¹⁴⁴⁾.

Liposome

It is a novel vesicular approach. Enhanced delivery of bioactive molecules through the skin by means of an ultra deformable vesicular carrier causes the prolonged and sustained effect of the drug. Protection of glucagon like peptide (GLP-1) from enzymatic degradation and improve pharmacological effects, liposomal formulations of GLP-1 were prepared using three types of lyophilized empty liposome such as anionic, neutral and cationic⁽¹⁴⁵⁾.

Aquasomes

Aquasomes are nanoparticulate carrier system these are three layered self assembled structures, comprised of a solid phase nanocrystalline core coated with oligomeric film to which biochemically active molecules are adsorbed with or without modification. Anti diabetic gliclazide drug is prepared through aquasomes and improved their oral bioavailability, sustained release over a period of 24 hours⁽¹⁴⁶⁾.

Emulsosomes

Emulsosomes are developed as novel lipid vesicular system with internal solid fat core surrounded by phospholipids bilayer. This technology is designed to act as vehicle for poorly soluble drugs. The drug is enclosed in the emulsosomes and provide prolong existence of drug in systemic circulation. Gliclazide is prepared through emulsosomes and their sustained action is improved⁽¹⁴⁷⁾.

Solid lipid nano particles

Lipophilic pharmaceuticals are prepared by using lipids as the polymers. These lipid nanoparticles are known as solid lipid nanoparticles. These consist of a solid hydrophobic core having a monolayer of phospholipids coating. The solid core contains drug dissolved or dispersed in the solid high melting fat matrix. Binary lipid matrix based solid lipid nanoparticles of repaginate significantly improves the oral bio availability of the drug⁽¹⁴⁸⁾.

Solid lipid micro particles (SLMs)

Sustained release SLMs of metformin hydrochloride prepared by melt-emulsification based on solidified reverse micellar solutions (SRMS) using a lipid derived from *Capra hircus* and Phospholipon® 90H. Researcher revealed that SLMs based on SRMS offer a new and better approach of delivering metformin hydrochloride and have significant higher glucose reduction than glucophage®⁽¹⁴⁹⁾.

Implants

Dental implant therapy has become increasingly common among patients with diabetes. The rising success of dental implants, along with the realized benefits of implant therapy has shifted current trends to accommodate patients with controlled diabetes as good candidates for treatment. Successful treatment results can be attained when placing implants on carefully selected patients with glycosylated haemoglobin levels (HbA1C) less than 8 percent and with possible prophylactic antibiotic administration⁽¹⁵⁰⁾.

Statin therapy

Type 2 diabetes is a major and independent risk factor for development of cardio vascular disease. Statin (inhibitors of 3- hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase) has beneficial effects on cardiovascular morbidity and mortality in both non diabetic and T2D. Recent analyses of both clinical trials and population based cohort studies suggest that the cardiovascular benefits of statin therapy outweigh the risk of developing T2D. High-intensity statin therapy alters the progressive nature of diabetic coronary atherosclerosis, yielding regression of disease in diabetic and non-diabetic patients⁽¹⁵¹⁾.

Stem cell therapy

Stem cell treatment of diabetes results in pronounced hypoglycaemic effect, i.e. decrease of blood sugar level, allowing reducing the dose of exogenous insulin by 50–70%. Stem cells hold tremendous potential as a source of insulin-producing cells that could be placed in a BioHub. Stem cells have the potential to become virtually any kind of cell. Scientists introduced the biliary cells to mature into islets. These islet structures produced insulin and c-peptide (a component of natural insulin production) in response to glucose. Transplanting these structures into diabetic mice dramatically improved blood sugar controls⁽¹⁵²⁻¹⁵³⁾.

Conclusions

Diabetes is a common disease where every individual needs unique care. Treatment and management of diabetes without any side effects is still a challenge for the medical system. Hence, search for a drug with low cost, more potential, and without adverse effects is being pursued in several laboratories around the world. People with diabetes and their families must be aware of the latest medical therapies and approaches, as well as

healthy lifestyle choices. Developing a community awareness campaign, early diagnosis of type 2 diabetes, routine care and monitoring of diabetes, patient education, psychological issues, developing and implementing guidelines, developing the diabetes workforce and services will help to manage the diabetes. Thus, a better understanding concerning the DM and novel approaches in formulation technology and therapy could guide the formulation scientists and clinicians towards the successful management of the disease.

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