Section A-Research paper

SELF-ASSEMBLED ULTRA DEFORMABLE VESICULAR SYSTEM LOADED DRUG FOR TARGETED DRUG DELIVERY FOR THE TREATMENT OF DIABETES MELLITUS FOR MULTI-TARGETED DRUGS.

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Abstract:
Type 2 diabetes mellitus (T2DM) affects a large population worldwide. T2DM is a complex heterogeneous group of metabolic disorders including hyperglycemia and impaired insulin action and/or insulin secretion. T2DM causes dysfunctions in multiple organs or tissues. Current theories of T2DM include a defect in insulin-mediated glucose uptake in muscle, a dysfunction of the pancreatic b-cells, a disruption of the secretory function of adipocytes, and an impaired insulin action in the liver. The etiology of human T2DM is multifactorial, with genetic background and physical inactivity as two critical components. The pathogenesis of T2DM is not fully understood. Animal models of T2DM have been proven to be useful to study the pathogenesis of, and to find a new therapy for, the disease. Although different animal models share similar characteristics, each mimics a specific aspect of genetic, endocrine, metabolic, and morphologic changes that occur in human T2DM. The purpose of this review is to provide the recent progress and current theories in T2DM and to summarize animal models for studying the pathogenesis of the disease. Diabetes Mellitus (DM) is a multi-factorial chronic health condition that affects a large part of the population and according to the World Health Organization (WHO), the number of adults living with diabetes is expected to increase. Since type 2 diabetes mellitus (T2DM) is suffered by the majority of diabetic patients (around 90–95%) and often the mono-target therapy fails in managing blood glucose levels and the other comorbidities, this review focuses on the potential drugs acting on multi-targets involved in the treatment of this type of diabetes. In particular, the review considers the main systems directly involved in T2DM or involved in diabetes comorbidities. Agonists acting on incretin, and glucagon systems, as well as on peroxisome proliferation-activated receptors are considered. Inhibitors that target either aldose reductase and tyrosine phosphatase 1B or sodium glucose transporters 1 and 2 are taken into account. Moreover, with a view at the multi-target approaches for T2DM some Phyto complexes are also discussed.

Keywords: Hyperglycemia, Type II diabetes, ultra deformable vesicles, Targeted drug delivery, Nanoparticles.

Introduction:

Diabetes Mellitus (DM) is a multi-factorial chronic health condition triggered by several genetic and/or environmental factors. Indeed, this pathology is characterized by solid familiarity and the frequency of diabetes varies in different ethnicities, such as black and Hispanic people, and some minorities, like American Indians and Natives of Alaska, are more likely to have diabetes for a specific genetic profile. The World Health Organization (WHO) Global report on diabetes shows that the number of adults living with diabetes has almost quadrupled since 1980 to 422 million adults and is expected to increase to 693 million by 2045. The disease is characterized by high blood sugar levels, due to a deficiency of concentration and/or of activity of insulin, the pancreatic hormone involved in managing glycemia. There is no cure for diabetes so far, but it can be treated and controlled. Pharmacological therapy and/or insulin may be required in order to maintain the blood glucose level as near as possible to normal and to delay or possibly prevent the development of diabetes-related health problems. However, disease management can be helped also by healthy eating and physical exercise.

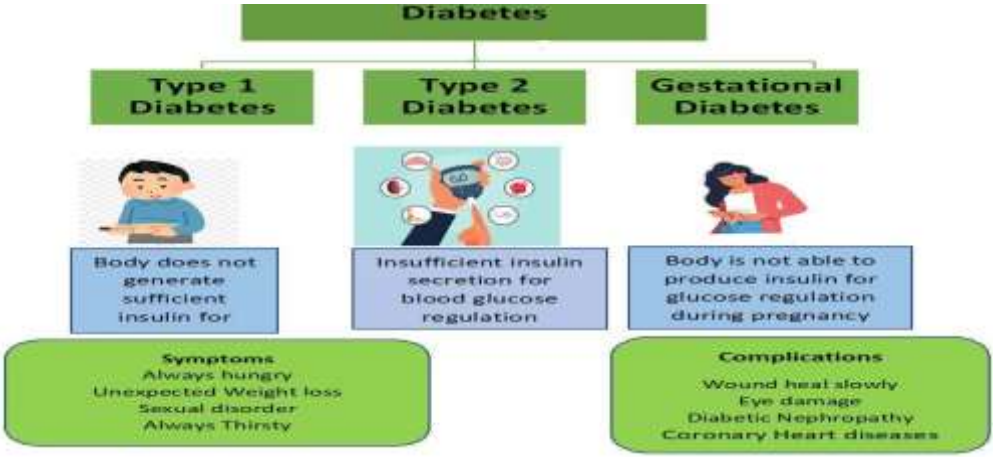
For determining the right therapy, the involved type of diabetes plays a key role and in 2018 American Diabetes Association (ADA) proposed the following classification:

1. Type 1 diabetes mellitus (T1DM): due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency;
2. Type 2 diabetes mellitus (T2DM): due to a progressive loss of β-cell insulin secretion frequently on the background of insulin resistance;
3. Gestational diabetes mellitus (GDM): diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt prior to gestation;
4. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young (MODY)), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation).

Since T2DM is suffered by the majority of diabetic patients (around 90–95%) This review focuses on the potential drugs acting on multi-targets involved in the treatment of this type of diabetes.

Type2DiabetesMellitus(T2DM)

Type 2 Diabetes Mellitus (T2DM) has been referred to for a long time as non-insulin dependent diabetes, or adult-onset diabetes characterized by insulin resistance, which could progressively worsen to absolute resistance, but in the past decade, the reduced β-cell function has been recognized as a key problem in T2DM. Indeed, in the past two decades



Type 2

Figure-1 Types of Diabetes, symptoms and its complications

T2DM emerged as a new and very serious health problem also in children. The studies carried out on children demonstrated the co-existence of obesity, insulin resistance, and β-cell dysfunction as observed in older T2DM patients. This association can be appreciated in Figure.

Pathogenesis of Type 2 Diabetes:

T2DM risk factors include a complex combination of genetic, metabolic, and environmental factors that interact with one another contributing to its prevalence. Although individual predisposition to T2DM due to non-modifiable risk factors (ethnicity and family history/genetic predisposition) has a strong genetic basis, evidence from epidemiological studies suggests that many cases of T2DM can be prevented by improving the main modifiable risk factors (obesity, low physical activity, and an unhealthy diet

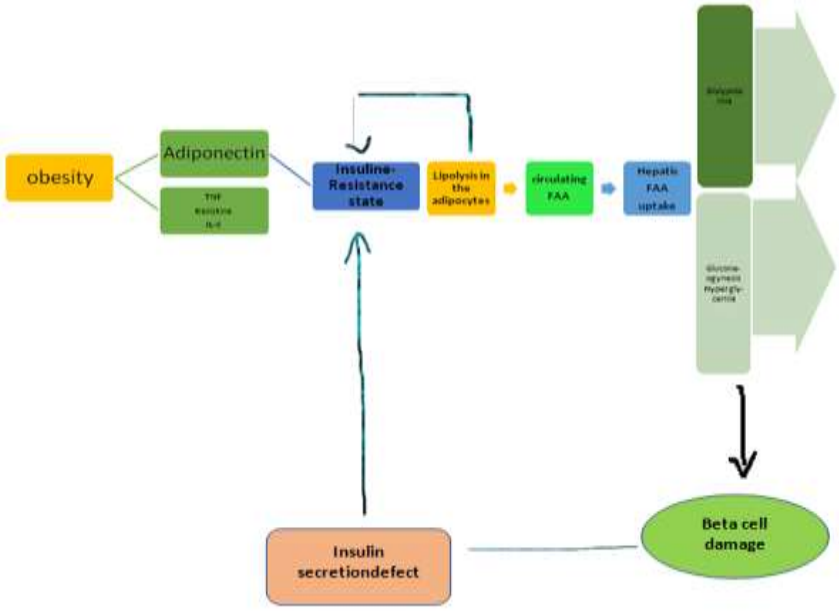
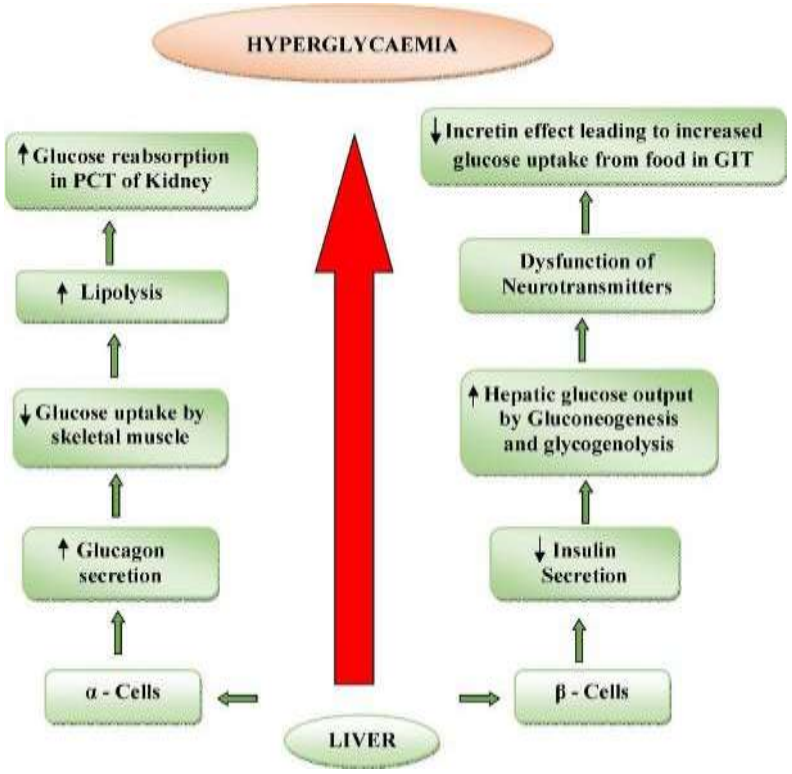


Figure-2 Pathophysiology of (T2DM)

T2DM risk factors include a complex combination of genetic, metabolic and environmental factors that interact with one another contributing to its prevalence. Although individual predisposition to T2DM due to non-modifiable risk factors (ethnicity and family history/genetic predisposition) has a strong genetic basis, evidence from epidemiological studies suggests that many cases of T2DM can be prevented by improving the main modifiable risk factors (obesity, low physical activity and an unhealthy diet



Treatment Approach forType 2 Diabetes(T2DM):-

- Healthy eating.
- Regular exercise.
- Weight loss.
- Possibly, diabetes medication or insulin therapy.
- Blood sugar monitoring.

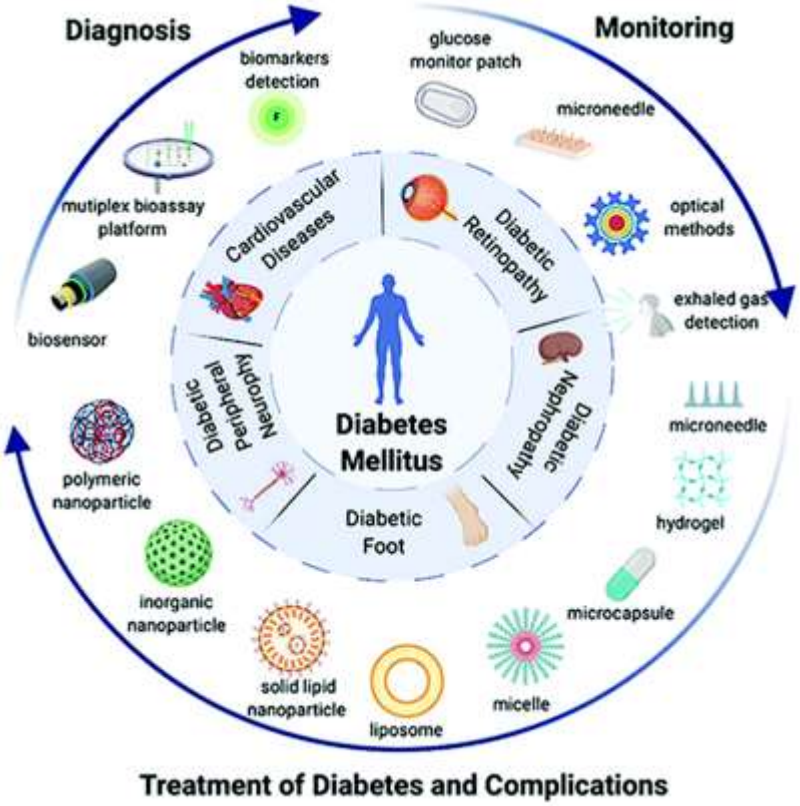


Figure-3 Different Treatment plans for Type 2 Diabetes

Animal models of Type II Diabetes for studying Disease Pathogenesis and Testing Therapeutic Agents

Animals a syndrome of insulin resistance and type 2 diabetes, with appearances alike to humans, comprise a wide range of type with genetic, experimental or nutritional connection. Some animals with inherent diabetes have pancreas with 'sturdy' beta cells capable of maintaining insulin secreting capacity characterized by severe hyperinsulinemia with only mild to moderate hyperglycaemia the life e.g., Zucker fatty rats (obese), KK mouse and (corpulent) cp rat group. At the other end of spectrum, some species possess 'brittle oral bile' pancreatic beta cells allowing only for transient insulin hyper secretion with short-term obesity. Subsequently, as a result of and affluent nutrition/ a uses, it induces emission pressure on beta cell which eventually leads to degranulation, apoptosis and overt hyperglycaemic state. At this point, the animals rapidly lose their beforehand collected adipose tissue, become kenotic and want insulin to survive. e.g., db./db. (diabetic)mouse, Zucker diabetic fatty (ZDF) rat, sand rat (Psammomas obsess) and obese rhesus monkeys11.The animals with 'brittle' pancreas closely simulate the disease evolution from insulin resistance to open-minded beta cell failure/frank hyperglycaemia as in human type 2 diabetes, than the animals with robust pancreas. Some of these animals with related phenotype of obesity and insulin resistance such as ZFR, ZDF rats and ob. /ob., db./db., KK and KK-Amice would be greatly helpful in identifying factors involved in obesity-induced diabetes (diabesity).Nevertheless, certain non-obese diabetic models are also used in the investigation of type 2 diabetes in beings that occur in the absence of obesity which allows the

dissociation of confounding obesity factors such as leptin deficiency and/or leptin confrontation and other associated hypothalamic factors from diabetes genes and factors [e.g., GK (Goto-Kakizaki) rats, Akita mouse]

New classes of drugs included in advanced therapy

This day and ageadaysthenewerclassesofdrugsusedforT2DMareassubsequent

i) Alpha glucosidase inhibitor
ii) Amylin agonists
iii) Incretin mimetics(GLP–1AgonistsandDPP–IVinhibitors)
iv) SGLT2antagonists/inhibitors

Some Drugs which used for the treatment of Type II Diabetes
Table-1Monotherapytherapyofantidiabeticdrugsfortreatmentof T2DM

	Name of the Drug	Pharmacological study	Outcome
1	Alpha glucosidase inhibitors (AGIs)	Voglibose, the alpha glucosidase inhibitor was intentional for controller over post prandial blood sugar (PPBS) and cardioprotective action in T2DM affected role.	Voglibose was found to have better c antidiabetic drugs over PPBS with minor cardiovascular risks control as linked with other
2	Amylin analogs	Pramlintide, a new class of amylin similarity was assessed for its usefulness in postprandial hyperglycaemia and management of weight in patients of T2DM	Pramlintide slowed the rate of gastric emptying, suppressed the secretion of glucagon after food intake, enlarged satiety and summary the proportion of food intake
3	GLP-1Agonists	Exenatide long acting release (LAR) administered weekly once was evaluated as an add-on drug to the regular dose of metformin to T2DM affected role for a time period of 8 months.	Exenatide improved the FBS, HbA1c, body index and lipid shape excluding the triglyceride level
4	Dipeptidyl Peptidase - IV inhibitors	In vitro study for the mechanism of binding trelagliptin with DPP – IV enzyme was calculated	Trelagliptin showed a sustained efficacy on once a weekly dose. Trelagliptin was found to be a reversible, substrate-competitive and slow binding DPP – IV inhibitor with a non-covalent interface..
5	SGLT2inhibitors	The hypoglycemic effects and control over other diabetes linked adverse side possessions of canagliflozin were evaluated	It also reduced the cardiovascular hazard connected with T2DM.

Table-2 Combination therapy of antidiabetic drugs for treatment of T2DM

	Name of the Drugs
1	Metformin and Sulfonylureas/ acarbose/ thiazolidinedione/ glinides
2	Gliclazide and/or Metformin and/or Acarbose
3	Alpha glucosidase inhibitors and DPP-IV inhibitors
4	Repaglinide
5	Alpha glucosidase inhibitor (Voglibose) and Glimepiride or Metformin
6	Alpha glucosidase inhibitor (Voglibose) or Metformin with Insulin
7	DPP – IV inhibitors with sulfonylureas

Table-3 Different reports on Novel Drug Delivery of Anti Diabetic drug delivery for (T2DM)

	Type of delivery system	**Class of drug**	**Name of drug**	**Polymer used**
1	Liposomes	Biguanides	Metformin	Glycerophosphate–ChitosanMicro complexation(GP/CHMicro complex
2	Niosome	Biguanides	Metformin	Cholesterol,span40,Span60,diacetylphosphate
3	Nanoemulsion	Repaglinide	InsulinSecretagogues	Span80,Tween80,oliveoilandacetone
4	Nano formulations in Transdermal patches(TDPs)	Biguanides	Metformin	Propylene glycol, Polymethacrylic acid and soya Lecithi
5	Nanocrystal	Sulfonylureas	Gliclazid	D,L-lactide-coglycolide) [PLGA] second generation nanocrystal, 0.5% w/v poloxamer -188
6	Transferosomes	hyperglycemia	Repaglinide	Tween80,Span 80, soya lecithin

Future Prospects:

Scientists and scholars have recently become interested in the Transferosomes Vesicular System. It is highly sought after for targeted drug administration through the subcutaneous route and deeper skin penetration due to its ultra-deformable properties, nano-size particles, and deformable system. In comparison to Ethosomes and Transferosomes, Liposomes, and Phytosomes, edge activator has been shown to have superior permeation and penetration properties. It is also appropriate for medicines with high and low molecular weights as well as hydrophilic and hydrophobic compounds. This new vesicular system is in great demand both now and in the future. There isn't presently a commercial formulation for nanoparticles (also known as Transferosomes) because scientists and researchers are still researching them. Transferosomes can also be loaded into novel drug delivery systems such as Patches Tablets, gel, injection form. Thus, the Transferosomes vesicular system has a lot of potential to use as a carrier for subcutaneous drug delivery. Different bioactive can easily be incorporated into

ultra-deformable vesicular systems such as Transferosomes for targeted delivery for the treatment of Type II Diabetes.

Conclusion:

The rising pattern of sedentary lifestyle and the higher incidence of obesity has contributed to an ever-increasing number of patients with diabetes, generating a massive demand for anti-diabetic medication and prompting companies to invest more on research and development for developing targeted formulations. Nanotechnology guarantees to bring in plenty of genuine ground breaking therapeutic advancements in our daily existence. Years of comprehensive nano formulation research have contributed immensely to substantial progress in the advancement of nanoparticulate drug delivery systems for anti-diabetic drugs. Long- term safety concerns and ethical issues related to nano formulations along with the latest FDA guidelines for the regulation of the said products needs to be implemented in order to facilitate the safety of such products to enhance their efficacy. Active targeting strategies involving the functionalization of suitable ligands or combinatorial drug therapy involving two or more antidiabetic drugs could suitably regulate glucose levels for longer periods of time. Such perpetual technological advances in nanotechnology offer compelling prospects in the foreseeable future regarding the development of an efficient glucose-lowering therapeutic modality.

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