

Review

Type II diabetes mellitus: a review on recent drug based therapeutics

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ABSTRACT

Diabetes mellitus (DM) is a metabolic disorder that occurs in the body because of decreased insulin activity and/or insulin secretion. Pathological changes such as nephropathy, retinopathy, and cardiovascular complications inevitably occur in the body with the progression of the disease. DM is mainly categorized into 2 sub-types, type I DM and type II DM. While type I DM is generally treated through insulin replacement therapy, type II DM is treated with oral hypoglycaemics. The major drug therapy for type II DM comprises of insulin secretagogues, biguanides, insulin sensitizers, alpha glucosidase inhibitors, incretin mimetics, amylin antagonists and sodium-glucose co-transporter-2 (SGLT2) inhibitors. Dual drug therapies are often recommended in patients who are unable to achieve therapeutic goals with first line oral hypoglycaemic agents as monotherapy. Inspite of the appreciable therapeutic benefits, the conventional dosage forms depicts differential bioavailability and short half-life, mandating frequent dosage and causing greater side effects leading to therapy ineffectiveness and patient non-compliance. Given the pathological complexity of the said disease, nanotechnology-based approaches are more enticing as it comes with added advantage of site-specific drug delivery with higher bioavailability and reduced dosage regimen.

In the present review article, we have made an attempt to explore the pathophysiology of type II DM, the conventional treatment approaches (mono and combination therapy) as well as the nano based drug delivery approaches for the treatment of type II DM.

1. Introduction

Diabetes mellitus (DM) is a major public health issue affecting more than 400 million people worldwide [1]. This metabolic disorder progressively leads to chronic microvascular, macrovascular and neuropathic life threatening complications. DM is caused either by deficiency of insulin secretion, damage of pancreatic β cell or insulin resistance related to non-use of insulin. Inclination to sedentary lifestyle may be the major reason for the continual rise in the number of diabetic patients globally which is expected to strike 366 million in 2030 in the elderly population (>65 years) [2]. The various complications associated with DM includes nephropathy, neuropathy, cardiovascular and renal complications, retinopathy, food related disorders and so on. Type 1 DM and type 2 DM are the 2 types of DM. Type 1 DM is an autoimmune disorder that affects pancreatic cells which reduces or impairs the production of insulin while type 2 DM is a result of impairment of pancreatic beta cells that hinder the individual's ability to use insulin [3].

The major conventional classes of drugs for the treatment of hyperglycemia includes sulfonylureas (enhance release of insulin from pancreatic islets); biguanides (reduces hepatic glucose production); peroxisome proliferator-activated receptor- γ (PPAR γ) agonists (boosts the action of insulin); α -glucosidase inhibitors (interferes with absorption of glucose in the gut) [4]. These classes of drugs are either administered as monotherapy or given in combination with other hypoglycaemics. Severe hypoglycemia, weight gain, lower therapeutic efficacy owing to improper or ineffective dosage regimen, low potency and altered side effects due to drug metabolism and lack of target specificity, solubility and permeability problems are the major drawbacks associated with the use of the above mentioned conventional drugs [5]. Despite the advent of promising anti-hyperglycemic agents, the major challenges in efficient diabetes treatment include optimizing the existing therapies to guarantee optimum and balanced glucose concentrations, as well as reducing long-term diabetes-related complications [6]. In such a scenario, nanoformulations have an established

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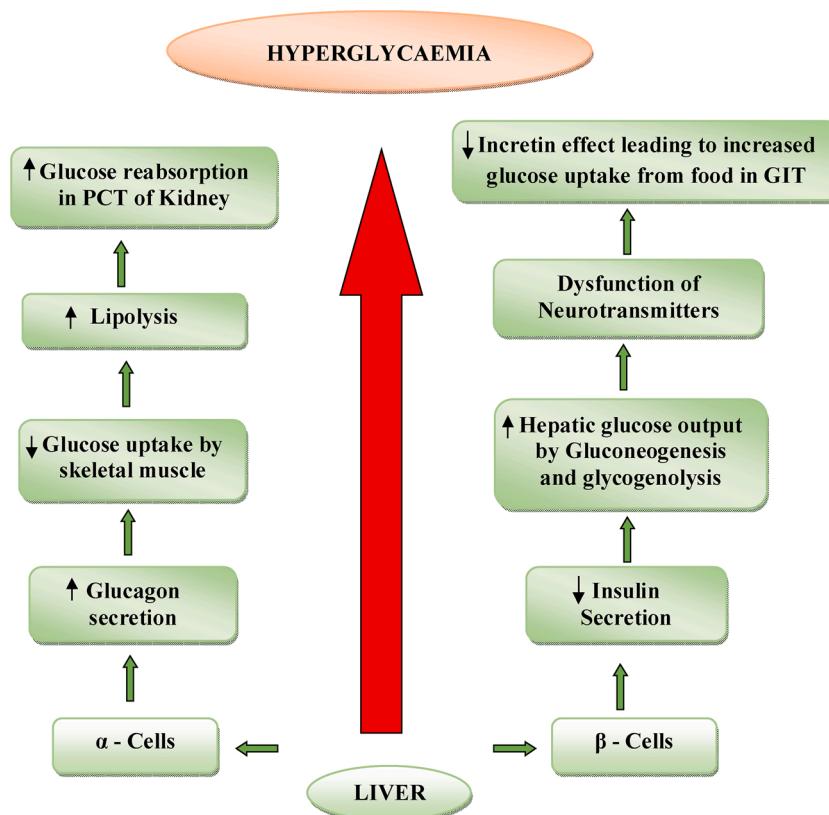


Fig. 1. Pathophysiology of T2DM – Ominous octet.

history in circumventing the stated issues related to the conventional drug usage [7]. Nanoformulations not only boost the drug's solubility but also have numerous benefits such as reduced dosage, rapid onset of action, controlled drug release profile, less side effects, optimized drug delivery, expanded drug half-life, minimized patient variability and optimized bioavailability and can thus resolve several of the drawbacks of current anti-diabetics [8]. Most significantly, it has been reported elsewhere that nanoformulations often work at molecular level to promote cellular drug uptake or disrupt efflux mechanisms such as the P-glycoprotein (P-gp) pump or target particular receptors that further strengthen the pharmacokinetics and pharmacodynamics profile of numerous anti-diabetic molecules [9,10].

This review explores the current conventional drugs used in the treatment of type 2 DM, the associated limitations related to their usage and the cutting edge novel nanoformulations that are under continual research for circumventing the stated drawbacks of the conventional drug use.

2. Pathophysiology of diabetes

The homeostasis of glucose in the body is maintained by a number of hormones. However two hormones namely, insulin and glucagon play a dominant role in the regulation of glucose homeostasis [11]. Insulin is secreted by β cells when the concentration of glucose rises. Insulin decreases the level of blood glucose either

- By inhibiting the production of glucose from liver by glycogenolysis and gluconeogenesis [12], or
- By increasing the uptake of glucose by liver, muscle and fat tissue [12].

Glucagon is secreted by α cells of pancreas when the concentration of glucose is low. Glucagon acts by

- Antagonizing the effect of insulin by enhancing the processes like glycogenolysis and gluconeogenesis in liver [13].
- In addition to glucagon, cortisol and catecholamines also increases the plasma glucose levels [13].

Other hormones which are involved in maintenance of normal glucose level are amylin (a 37 amino acid peptide), glucagon like Peptide – 1 (GLP-1) (a 30 amino acid peptide) and Glucose dependent insulinotropic polypeptide (GIP) (a 42 amino acid peptide) [14,15].

Amylin is secreted along with insulin. It decreases gastric emptying, which enhances glucose absorption after a meal intake. GLP and GIP are incretin or peptide derived from the gut. These incretins facilitates the synthesis and secretion of insulin from β cells of pancreas [16].

Glucose is not absorbed from intestine or by cells requiring energy freely. So the distribution of glucose to the cells is done by glucose transporters. The Glucose transporters are a family of membrane bound glycoproteins and are classified into two types [17].

- Sodium glucose co-transporter (SGLT)
- Facilitative glucose transporter (GLUT)

Diabetes mellitus is categorized into two major sub-types and the causes associated remains differential [18].

- Type – I DM (T1DM): The immune system mistakenly attacks the β cells of pancreas where genes play a vital role.
- Type – II DM (T2DM): Interplay of genetics and lifestyle factors plays a vital role. Being obese or overweight increases the associated risks.

Pathophysiology of T2DM may include any one or combination of any mechanisms of “ominous octet” as represented in Fig. 1 and as outlined below: [19]

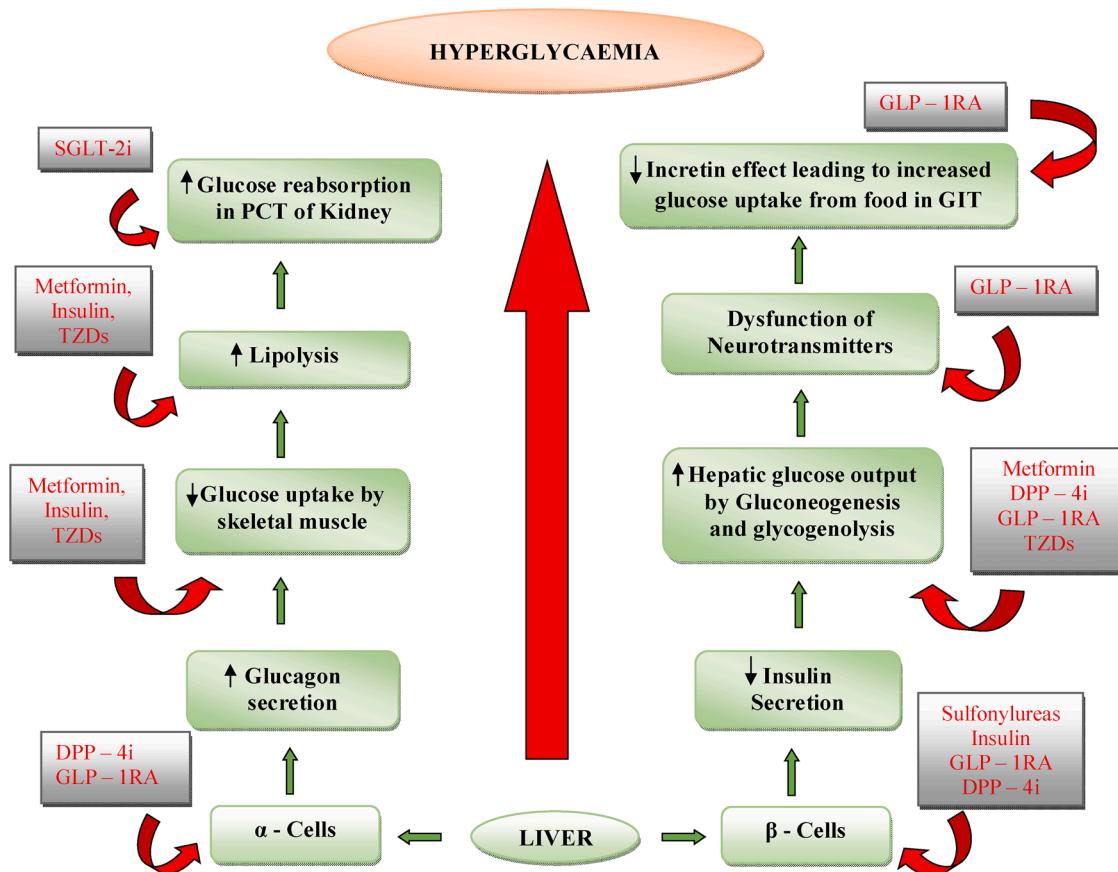


Fig. 2. Targets of treatment for T2DM [TZDs – Thiazolidinediones, DPP – 4i – Dipetidyl peptide – 4 inhibitor, GLP-1RA – Glucagon like peptide – 1 receptor agonist, SGLT-2i - Sodium–Glucose co-transporter 2 inhibitor].

- i) Reduced secretion of insulin from β cells of islets of langerhans
- ii) Elevated glucagon secretion from α cells of islets of langerhans
- iii) Increased production of glucose in liver
- iv) Dysfunction of neurotransmitter and resistance of insulin in the brain
- v) Increase in lipolysis
- vi) Increase in reabsorption of glucose by kidney
- vii) Reduction of effect of incretin in the small intestine
- viii) Impairment or decreased uptake of glucose by peripheral tissues like skeletal muscle, liver and adipose tissue
- Gestational diabetes occurs due to hormonal changes during pregnancy. The placenta produces hormones that make cells less sensitive to the effects of insulin [20,21].
- Genetic mutations can lead to diabetes mellitus like monogenic diabetes is caused by mutations in a single gene. The most

common type of monogenic diabetes is neonatal diabetes and maturity onset diabetes of the young (MODY) [22].

- Cystic fibrosis produces thick mucus that causes scarring in the pancreas from making enough insulin [23].
- Hemochromatosis causes the body to store too much of iron. If the disease is not treated, iron can build up in and damage the pancreas and other organs [24].
- Some hormonal diseases causes the body to produce large amount of hormones which sometimes cause insulin resistance and causes diabetes.
 - o Cushing's syndrome occurs when the body produces too much cortisol, often called as stress hormone [25].
 - o Acromegaly occurs when the body produces too much of growth hormone [26].
 - o Hyperthyroidism occurs when the thyroid gland produces too much thyroid hormone [27].
- Damage or removal of pancreas, like pancreatitis, pancreatic cancer and trauma can harm the beta cells or can make them less able to produce less insulin, resulting in diabetes. If the damaged pancreas is removed, diabetes will occur due to the loss of the beta cells [15,28,29].
- Certain medicines can affect beta cells or leads to disruption in the beta cell functioning. These medicines include niacin, certain diuretics, anti-seizure drugs, psychiatric drugs, and medications for treating HIV, pentamidine, glucocorticoids, anti – rejection medicines and statins even [15,30,31].

There are various factors that increases the risk for diabetes [32]. The dominant factors are detailed below:

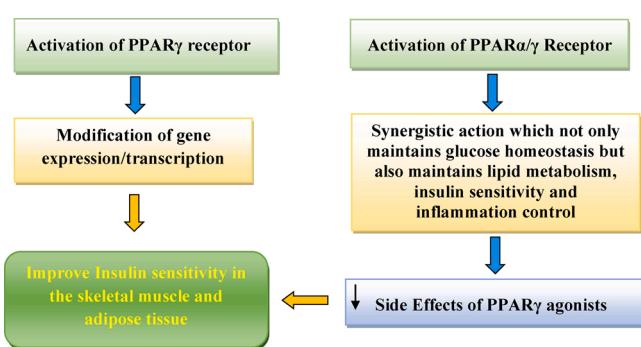


Fig. 3. Schematic Mechanism of action of Peroxisome Proliferator Activated Receptor (PPAR) agonists.

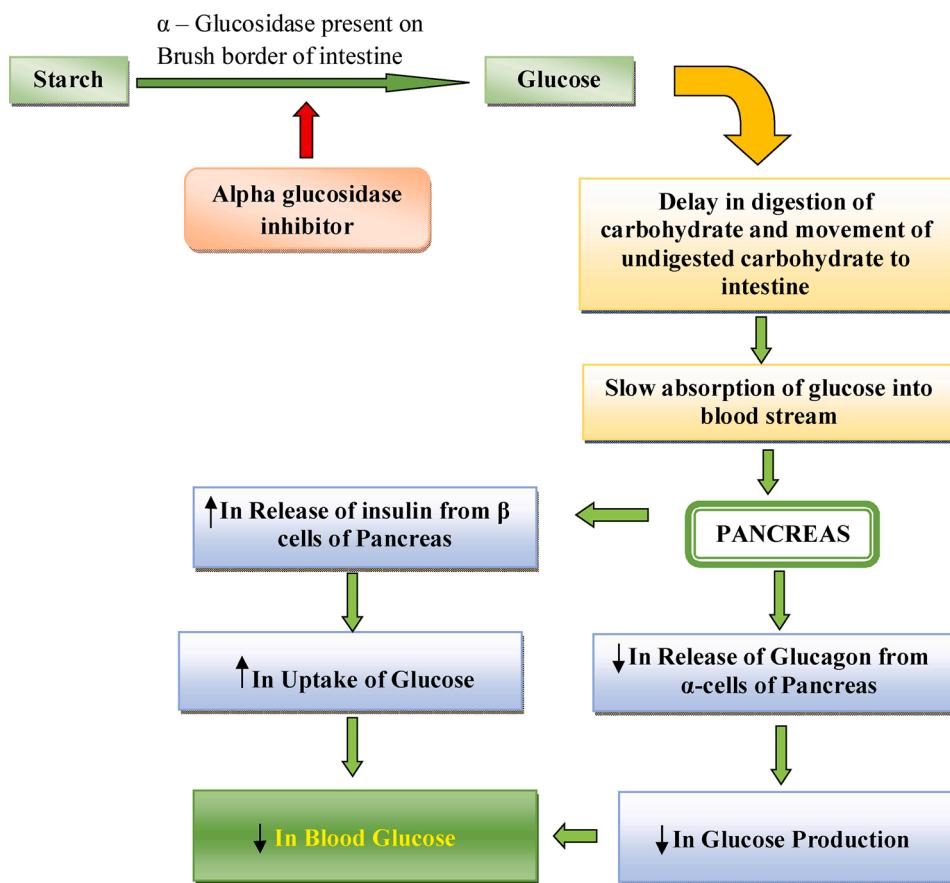


Fig. 4. Schematic mechanism of α – glucosidase inhibitor to lower the blood glucose level.

- In case of T1DM, being a child or teenager, risk of diabetes increases if the parent or sibling is diabetic [33].
- In case of T2DM, risk increases due to certain factors like being overweight, diet habits, age more than 45yrs, having history of diabetes in the family, physically less active, or having pre-diabetes or gestational diabetes, high cholesterol or triglycerides levels [34–37].
- Risk of gestational diabetes increases if the person is overweight with the age over 25 years, having gestational diabetes during past pregnancy, given birth to a baby weighing around more than 9 pounds, have a family history of T2DM and have polycystic ovary syndrome (PCOS) [38].

Diabetes has a lot of complications associated with it as high blood sugar damages organs and tissues throughout the body. The longer the body deals with high blood sugar levels, the risk of additional complications surfaces up. Complications of diabetes can be microvascular which includes nephropathy, retinopathy, loss of vision and macrovascular like heart diseases, heart attack, stroke, and neuropathy, infections and sores that don't heal bacterial and fungal infections, depression and dementia [39].

Any person with remarkable symptoms of diabetes mellitus or at a risk of it should be tested regularly.

For diagnosing prediabetes and diabetes, several blood tests can be done, namely:

- Fasting plasma glucose (FPG): helps in measuring blood glucose after fasting for 8 hours.
- HbA1C test: helps in measuring blood sugar levels over the period of previous three months.

For diagnosing gestational diabetes, blood tests are done within 24th and 28th week of pregnancy, and tested for glucose challenge test and three hour glucose tolerance test [20,40].

3. Therapeutic approaches in non-insulin treatment for type 2 diabetes mellitus

A number of non-insulin based oral therapies have emerged for the treatment of type 2 DM (Fig. 2). These are categorized under the following sub-headings:

- 1 Insulin Secretagogues
- 2 Biguanides
- 3 Insulin Sensitizers
- 4 Alpha Glucosidase Inhibitors
- 5 Incretin mimetics
- 6 Amylin antagonists
- 7 SGLT2 inhibitors

• **Insulin secretagogues:** These category of drugs (especially sulfonylureas and metiglinides) act by increasing the secretion of insulin from pancreas by binding to sulfonylurea receptor (SUR) of ATP sensitive potassium channel on pancreatic β cells [41]. 1st generation sulfonylurea are Tolbutamide, Chlorpropamide, Tolazamide, Acetohexamide and 2nd generation sulfonylurea includes Glibenclamide, Glipizide, Glimepiride [42]. Development of 2nd generation sulfonylurea was due to increased potency, more rapid onset of action, shorter plasma half-lives and longer duration of action. Common side effects of sulfonylurea includes sign of low blood sugar level such as dizziness, sweating, confusion and nervousness [43]. It may also include hunger, weight gain, skin reaction, stomach upset and dark colored urine.

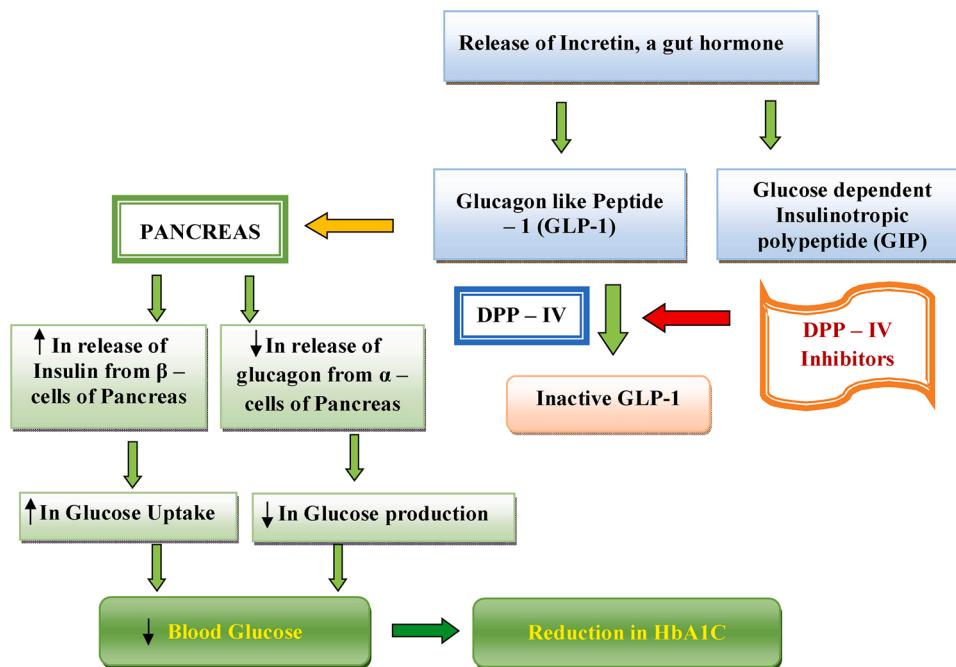


Fig. 5. Schematic Mechanism of Incretin mimetics in lowering the blood glucose and HbA1C.

Metiglinide is the prototype molecule that is a derivative of benzoic acid of non-sulfonylurea moiety of Glibenclamide. These agents exert their effect by closing the ATP sensitive potassium channel found on plasma membrane of pancreatic β cells [43]. Other molecules used in this category are Repaglinide and Nateglinide [44].

- **Biguanides:** It works by improving body's response to natural insulin, decreases the absorption of glucose from the intestine and reduces the amount of glucose produced by liver. Biguanides reduce hepatic glucose output by decreasing gluconeogenesis and stimulating glycolysis. They increase the insulin signaling by increasing the insulin receptor activity [45]. Unlike insulin secretagogues, these molecules don't influence the insulin secretion directly. Different molecules in this category are Metformin, Phenformin and Buformin.

Phenformin and Buformin were withdrawn from clinical use due to a high incidence of associated lactic acidosis whereas Metformin has a much lower risk of lactic acidosis, hence widely used [46]. Biguanides don't cause hypoglycemia or induce weight gain, show anti-hypertriglyceridemic effect and vasoprotective properties. Biguanides block the breakdown of fatty acids through activation of AMP-dependent protein kinase [47]. But biguanides have common adverse effect of gastrointestinal distress, including diarrhea, cramps, nausea, vomiting, and increased flatulence. Its Long-term use is associated with decreased absorption of vitamin B₁₂ [48].

- **Insulin Sensitizers:** The insulin sensitizers are also known as Peroxisome Proliferator Activated Receptor agonists (PPARs). PPARs are the regulators of protein and carbohydrate metabolism and maintain the glucose homeostasis. These are nuclear hormone receptor

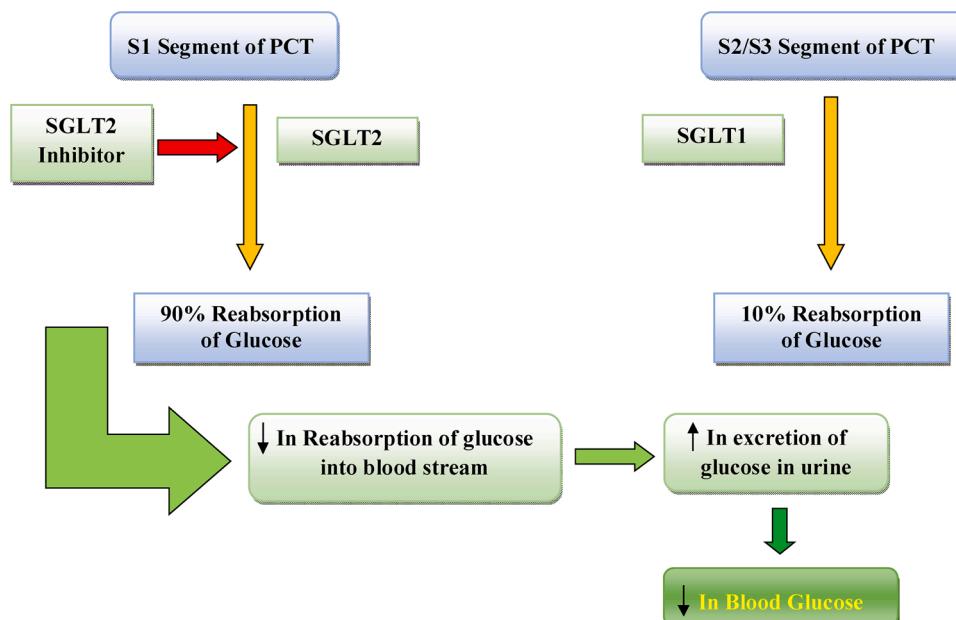


Fig. 6. Schematic representation of mechanism of action of SGLT2 Inhibitors.

Table 1

Monotherapy of antidiabetic drugs for the treatment of T2DM.

Name of the drug	Pharmacological study	Outcome	Reference
Alpha Glucosidase inhibitors (AGIs)	Voglibose, the alpha glucosidase inhibitor was studied for control over post prandial blood sugar (PPBS) and cardioprotective action in T2DM patients.	Voglibose was found to have better control as compared with other antidiabetic drugs over PPBS with lesser cardiovascular risks. Its efficiency was established in pre-diabetic elderly patients with hepatic impairment or renal complications where other antidiabetic drugs failed to show the desired therapeutic action.	[91]
	The antidiabetic activity acarbose, voglibose and miglitol were studied and compared for antihyperglycemic effect along with their propensity to develop cardiovascular risks associated with T2DM.	Voglibose had inhibitory effect on glucagon secretion. It was also effective in reduction of HbA1c and reduction of cardiovascular risks. As compared to acarbose and miglitol, voglibose demonstrated very less drug reaction owing to the administered low dose.	[92]
	Study on the effect of voglibose, before and after meal in patients with and without impaired glucose tolerance and compared with other alpha glucosidase inhibitor like miglitol and acarbose.	The efficiency of blood glucose lowering capacity of voglibose was significant as compared to control group when administered before meal.	[93]
	Miglitol was assessed for reduction in postprandial glucose level and gene expression of inflammatory cytokines.	Miglitol suppressed the gene expression for interleukin - 1 β and putative inflammatory cytokines S100a4/6/8/9 by reducing fluctuation in plasma glucose level.	[94]
Amylin analogs	A crossover investigation was done to assess the effectiveness of two alpha glucosidase inhibitor, voglibose and acarbose in T2DM patients.	Acarbose inhibited pancreatic α -amylase which metabolized polysaccharide like starch, whereas voglibose was more specific in its action against disaccharides like maltose and sucrose. In the crossover study, acarbose (50 mg) and voglibose (0.3 mg) showed the similar effect on postprandial hyperglycemia.	[95]
	Pramlintide, a new class of amylin analogue was assessed for its efficacy in postprandial hyperglycemia and management of weight in patients of T2DM.	Pramlintide slowed the rate of gastric emptying, suppressed the secretion of glucagon after food intake, increased satiety and reduced the rate of food intake.	[96,97]
GLP-1 Agonists	Study on the available molecules of GLP-1 agonist which are resistant to degradation by DPP-IV enzyme. The detail mechanism of pharmacological effect, pharmacokinetics of DPP-IV resistant analogues were discussed.	The available DPP-IV resistant analogues of GLP-1 molecules include sexenatide, liraglutide, semaglutide, efglاغناتide, exenatide ER, Itca 650 (Intarcia), dulaglutide, albiglutide and lixisenatide. Dulaglutide and albiglutide are novel drug molecules which are administered once a week. Efglاغناتide is the longest acting GLP-1 analogue which is administered once a month. It not only patient compliant but also it overcomes the problems related to adverse reactions like injection site reactions nausea and gastrointestinal disorders. Itca 650 was under phase II clinical trial but it was rejected by FDA due to issues related to clinical response letter (CRL), but it was the first non-injection type-2 therapy. Exenatide and lixisenatide are short acting analogues which mostly control PPBS whereas the long acting analogues like liraglutide, exenatide ER, albiglutide and dulaglutide are recommended for controlling the fasting blood glucose (FBS) level.	[98]
	Exenatide was the first marketed GLP-1 agonist as antidiabetic drug. It was administered twice a day due to fast clearance. So to prolong its effect, four exenatide analogues were produced by modified lipid chain ligation. C1 – C4 were analysed for their plasma stability and antihyperglycemic effect.	Among the four analogues of exenatide, C2 showed the highest plasma half-life. The hypoglycaemic effect was pronounced to be more for C2 analogue which was observed to be more than exenatide and liraglutide. Insulinotropic activity and glucose lowering capability of C2 analogue was comparable to exenatide and liraglutide. The peptide modified exenatide analogues proved to be long acting analogues showing antidiabetic activity with lowering of dosing frequency to once daily injection.	[99]
	Exenatide long acting release (LAR) administered weekly once was evaluated as an add-on drug to the regular dose of metformin to T2DM patients for a time period of 8 months.	Exenatide improved the FBS, HbA1c, body index and lipid profile except the triglyceride level. So exenatide LAR administered weekly once with metformin could act as a cardioprotective drug in T2DM patients.	[100]
	The glycemic efficacy, cardioprotective activity and safety of exenatide QW once a week was studied in T2DM for a time span of seven years.	There was a marked improvement in HbA1c and cardiovascular risk factors including body weight, diastolic blood pressure, total cholesterol, low-density lipoprotein cholesterol (LDL) and high-density lipoprotein cholesterol (HDL). Treatment with exenatide QW for seven years showed a sustained improvement of glycaemic control and the associated cardiovascular risk factors.	[101]
Lixisenatide	The effect of exenatide QW (once a week) and liraglutide were studied and compared with insulin naïve T2DM patients for glycated hemoglobin and weight measures for a time period of one year.	During one year of retrospective cohort analysis involving exenatide i.e. exenatide QW (once a week) and liraglutide once daily with insulin naïve T2DM patients, the reduction and control of glycated hemoglobin was found to be same with both the GLP-1 agonists but it was more reduced in insulin naïve patients. Weight gain, the side effect of insulin therapy, was reduced with GLP-1 agonists. During the trial, liraglutide produced gastrointestinal adverse side effects as compared to exenatide QW therapy.	[102]
	Lixisenatide was assessed for efficacy and safety dosed once a day in T2DM patients who on dual therapy of sulfonylureas and metformin.	Efficacy of Lixisenatide at 20mcg dose, once a day was found to reduce the FBS and PPBS along with body weight significantly in the treated patients as compared to those in placebo group. The incidence of adverse side effects and episodes of hypoglycemia was lesser as compared with exenatide (10mcg twice a day).	[103]
	Lixisenatide with basal insulin therapy was compared with T2DM patients with sulfonylureas with basal insulin. The study was carried out in T2DM patients wanted to fast during the month of Ramzan 2017.	The incidence of hypoglycemia was reduced in fasting T2DM patients during ramdan fasting as compared with patients on sulfonylureas and insulin dual therapy. The study demonstrated the safety and efficacy of lixisenatide with basal insulin for T2DM patients.	[104]

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Table 1 (continued)

Name of the drug	Pharmacological study	Outcome	Reference
	The study compared the efficacy and safety of lixisenatide (20mcg) with a DPP – IV inhibitor sitagliptin (100 mg) in T2DM patients maintained with metformin therapy. In this study novel Oxyntomodulin (OXM) derivatives were synthesized by incorporation of different residues at C terminus of GLP-1, Exenatide and glucagon to formulate hybrid peptides. The efficacy and safety study of semaglutide 1 mg (a GLP-1 receptor agonist) with canagliflozin 100 mg (an SGLT2 inhibitor) was conducted and compared in a double blind, randomized controlled trial in patients with T2DM. The efficacy, safety and cost utility of lixinatide with insulin was analysed in T2DM patients having uncontrolled sugar levels with other oral antidiabetic drugs	Lixisenatide showed a significant reduction in PPBS, HbA1c and weight in T2DM patients. The incidence of symptomatic hypoglycemia was less in case of oral lixisenatide as compared to sitagliptin. The glucagon exenatide hybrid peptide showed higher GLP-1 receptor activation properties than OXM. The peptide hybrid was able to reduce the blood sugar level, HbA1c and bodyweight in obese T2DM patients Semaglutide was found to be more efficacious and safer drug for T2DM, as the reduction of primary end point and secondary end point at the end of 52 weeks was found to be more in the group treated with semaglutide as compared to canagliflozin. Lixinatide was found much better as compared to basal insulin and premixed insulin in lowering the HbA1c, weight loss and incidence of hypoglycaemia. Lixinatide was also found to be cost effective treatment in T2DM as compared to insulin therapy	[106]
	Study on the long term effectiveness of liraglutide was conducted in T2DM patients with regard to reduction in BMI, body weight and HbA1c in female patients.	An effective reduction of body weight from 92.1 ± 20.5 kg to 87.3 ± 20.0 Kg ($p < 0.001$), BMI of -2.0 ± 3.1 Kg/m ² and HbA1c from $7.9 \pm 0.9\%$ to $7.0 \pm 0.7\%$ was noted in the study.	[108]
	The study was conducted for assessing the effect of DPP-IV inhibitor and alpha glucosidase inhibitor (AGIs) on gut microbiota and subsequently its effect in hyperglycemia.	DPP – IV inhibitors increased the abundance of bacterioidetes and promoted the functional shift in the gut microbiome. DPP- IV inhibitors modulated the composition of the gut microbiota, which was a new hypoglycaemic mechanism and an additional benefit of the said drug. Sitagliptin improved the HbA1c significantly and achieved the target of controlling the glycaemic parameters in T2DM patients who were not treated previously or who were poorly responsive to other antidiabetic treatments. Sitagliptin displayed good efficacy and well tolerated in such patients. Sitagliptin with glimepiride also improved the blood glucose control.	[109]
	The study compared the ameliorating effect of sitagliptin with other seven pre-existing antidiabetic drug therapies to lower blood glucose level in T2DM patients	Sitagliptin and pioglitazone showed similar type of reduction of HbA1c from baseline in patients with inadequate control with metformin therapy. Sitagliptin was more efficacious than pioglitazone in reduction of body weight and improvement of lipid profile.	[110]
	A comparative study was conducted to analyze the efficacy of sitagliptin Vs pioglitazone as add-on to metformin therapy in patients with uncontrolled glycemic parameters of T2DM	In this study, episodes of hypoglycemic attacks were relatively lesser in the group treated with saxagliptin as compared to glimepiride. Efficacy and tolerability of saxagliptin was higher in patient ≥ 65 years.	[111]
	A random, controlled study was carried out to evaluate the efficacy and safety of saxagliptin as compared to glimepiride in elderly patients with T2DM in which the adequate control of glycemic parameters with metformin was not achieved.	The efficacy of once a week trelagliptin was found similar to daily alogliptin, hence it can be inferred that trelagliptin can be a drug of choice as the dosing frequency is reduced and probability of patient compliance would be more.	[112]
	A random, parallel, double blind study was done to compare the safety and efficacy of trelagliptin, a once weekly oral DPP – IV inhibitor with daily oral alogliptin and placebo.	In this study, the dosing of once a week of trelagliptin was found to be more patient compliant in the form of reduction of dosing frequency. Trelagliptin showed a sustained efficacy on once a weekly dose.	[113]
	Study on the effect of switching the treatment of T2DM from daily dosing to once a week dosing of trelagliptin was studied.	Trelagliptin was found to be a reversible, substrate-competitive and slow binding DPP – IV inhibitor with a non-covalent interaction.	[114]
	<i>In vitro</i> study for the mechanism of binding trelagliptin with DPP – IV enzyme was studied.	The group treated with anagliptin showed increase in plasma GLP – 1 and GIP level after the test meal leading to lowering of glucose by increase in insulin secretion. In both the groups, gastric emptying delay was not observed.	[115,116]
	A new DPP – IV inhibitor, anagliptin was assayed by LC – HRMS for its effect on serum glucagon and GIP level which maintains the glucose homeostasis.	It was found that teneligliptin was a potent, competitive and long lasting DPP – IV inhibitor which showed good reduction in postprandial hyperglycemia and dyslipidemia post single and repeated administration.	[117]
	<i>In vitro</i> and <i>in vivo</i> effect of teneligliptin for hypoglycemic and dyslipidemic activity was evaluated after single and repeated administration.	Teneligliptin monotherapy significantly improved the glycemic control in patients with T2DM on hemodialysis. Teneligliptin reduced glycated albumin, HbA1c and fasting blood glucose level without severe precipitation of hypoglycemia. The HbA1c reduction was about 0.8 - 0.9% after administration of 12 weeks.	[118]
	Teneligliptin was assessed for efficacy and safety in T2DM patients with end stage renal disease.	Teneligliptin was efficacious in controlling the glycemic hemostasis, reducing the cardiovascular risks and improving the β cell functions.	[119]
	Teneligliptin a third generation DPP – IV inhibitor was assessed for the efficacy and safety in T2DM patients with inadequate glycemic control.	The study revealed a high level efficacy of teneligliptin with high tolerability and add-on therapy of metformin.	[120,121]
	A single centered observational study for efficacy and safety of Teneligliptin with metformin was conducted.	The overall reduction in HbA1c in all the groups were found to be similar. But in secondary outcome analysis, vildagliptin significantly reduced total cholesterol as compared to sitagliptin and saxagliptin group.	[122]
	The study was conducted to evaluate the efficacy of three DPP – IV inhibitors, namely sitagliptin, vildagliptin and saxagliptin.	Treatment of omarigliptin in T2DM patients showed significant reduction in HbA1c levels. Very low incidence of hypoglycemia was observed.	[123]
	Monotherapy of omarigliptin, once weekly DPP – IV inhibitor was evaluated by a random double blind trial study for glycaemic control and risk of hypoglycemia in T2DM patients.	Vildagliptin was found to be beneficial when administered as monotherapy or dual therapy with metformin or pioglitazone. The therapy was observed to be more efficacious in Asian elder patients.	[124]
	The benefit-risk assessment of alogliptin was done in Asian and non-Asian elder patients with T2DM along with renal or hepatic impairment, cardiovascular problems.	Canagliflozin showed reduction of blood sugar level significantly with reduction in body weight, systolic and diastolic blood pressure. It also reduced the cardiovascular risk associated with T2DM.	[125]
	The hypoglycemic effects and control over other diabetes associated adverse side effects of canagliflozin were evaluated.		[126]
SGLT2 inhibitors			[127]
			[128,129]

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Table 1 (continued)

Name of the drug	Pharmacological study	Outcome	Reference
PPAR γ agonist	COLOUR study was done to assess the efficacy and safety of Canagliflozin in overweight and obese T2DM patients.	The study reported the reduction in primary endpoint parameters such as HbA1c, FBS and PPBS. There was significant reduction in secondary endpoint parameters like reduction in body weight in terms of decrease in waist circumference, reduction in systolic and diastolic blood pressure at the end of 24 week study.	[130]
	A comparative study was conducted to assess the efficacy and safety of canagliflozin 100 mg Vs glimepiride in T2DM patients with inadequate control with metformin treatment.	As compared to glimepiride, canagliflozin showed increase in survival time period due to improvement in body weight, reduction in hypoglycemic episodes and reduction in microvascular and macrovascular adverse reactions in patients with inadequate control of diabetes due to metformin monotherapy.	[131,132]
	A comparative study of assessment of efficacy, glycemic control, weight loss and durability of glycemic control of canagliflozin Vs sitagliptin in T2DM patients.	In this comparative study, canagliflozin was found to reduce and maintain the HbA1c below threshold level for longer duration than those treated with sitagliptin. Loss of body weight was more in the group of canagliflozin as compared to sitagliptin.	[133]
	The efficacy and safety of dapagliflozin was assessed for its hypoglycemic effect in T2DM patients with inadequate control with metformin therapy.	Dapagliflozin was found to be selective SGLT2 inhibitor which prevented the renal reabsorption of glucose. It acted independent of insulin and showed significant reduction in hyperglycemia when co-administered with metformin.	[134–137]
	A meta-analysis of randomized trial was done to assess the efficacy and safety of dapagliflozin as a monotherapy in T2DM patients.	Dapagliflozin was well tolerated and reduced the glycemic factors like HbA1c, fasting blood sugar and body weight without causing hypoglycemia. It was observed that the risk of urinary tract infection and genital tract infection was increased.	[138]
	The efficacy, safety and tolerability of empagliflozin was assessed from a pooled data of T2DM patients.	Empagliflozin 10 mg and 25 mg were well tolerated and also proved efficacious in maintaining the glycaemic control. Incidence of hypoglycemia was less except the groups treated with sulfonylurea or insulin. The adverse effect of urinary tract infection and genital tract infection was higher in groups treated with empagliflozin than placebo.	[139,140]
	A pooled analysis of efficacy and safety of ertugliflozin 5 mg or 15 mg once a day were done as monotherapy or in combination with other antidiabetic drugs.	Ertugliflozin showed reduction in HbA1c from the placebo group in the 26 week study. Ertugliflozin also reduced the body weight and systolic blood pressure, so caused lowering of cardiovascular risk. The episodes of hypoglycemia, mycotic infection or urinary tract infection were similar as compared to placebo or other antidiabetic drugs.	[141,142]
	The efficacy and safety of remoglitazone was compared with dapagliflozin in T2DM patients with inadequate glycaemic control by monotherapy of metformin	Remoglitazone etabonate improved the glycaemic control in patients with inadequate control due to metformin monotherapy. Remoglitazone etabonate 100 mg and 250 mg were well tolerated, effective and non-inferior to dapagliflozin 10 mg QD.	[143]
	Pioglitazone, is one of the PPAR γ agonist used in treatment of T2DM due to its adverse effects. A systematic review was conducted for the comparison of pioglitazone monotherapy with other therapies used in T2DM.	Pioglitazone reduced the HbA1c and fasting blood sugar and body weight. There was a significant improvement in blood pressure and triglyceride levels with less episodes of hypoglycemia. Pioglitazone can be a drug of choice in insulin resistant T2DM patients with dyslipidemia, hypertension and history of cardiovascular disease.	[144]
	Saroglitazar is a dual PPAR α/γ agonist used approved for the treatment of diabetic dyslipidemia. A study was conducted to evaluate the reduction in atherogenic lipids through PPAR α/γ agonism.	Saroglitazar effectively reduced hypertriglyceridemia and improved insulin sensitivity along with β -cell function by reduction in gluco-lipotoxicity and possibly directly through PPAR γ agonism in patients of T2DM with hypertriglyceridemia.	

superfamily of ligand activated transcription factors [49]. These receptors are of three sub-types i.e. PPAR α , δ and γ . PPAR γ is specific for glucose homeostasis. PPAR γ agonists are generally thiazolidinedione and are known as “glitazones” [50]. Glitazones increase the sensitivity of cells to insulin. They also decrease the systemic fatty acid production and their uptake. PPAR γ activation improves glucose uptake by skeletal muscles and decreases the glucose production by retarding the gluconeogenesis [51] (Fig. 3). The first generation molecules under this category are Pioglitazone, Rosiglitazone and Ciglitazone. These are associated with common side effects like edema, weight gain, macular edema and heart failure. They may cause hypoglycemia when combined with other anti-diabetic drugs as well as they decrease hematocrit, decrease hemoglobin levels and increase bone fracture risk [52]. Recently dual PPAR α/γ agonists are discovered to be antidiabetic activity. PPAR α and PPAR γ receptor activation produces synergistic action and maintains the lipid metabolism, insulin sensitivity, inflammation control. The dual therapy reduces the side effects of PPAR γ agonists. Muraglitazar, Tesaglitazar, Aleglitazar, Ragaglitazar, Naveglitazar and Saroglitazar are example of dual PPAR α/γ agonists [53]. The use of Muraglitazar was withdrawn from clinical trials due to cardiotoxicity [54].

The use of first line drugs for the treatment of DM were substituted by the second line drugs due to the prevalent side effects associated with the former class of drugs [55].

4. New classes of drugs included in advanced therapy

Now a days the newer classes of drugs used for T2DM are as following

- i) Alpha glucosidase inhibitor
- ii) Amylin agonists
- iii) Incretin mimetics (GLP – 1 Agonists and DPP – IV inhibitors)
- iv) SGLT2 antagonists/ inhibitors

4.1. Alpha-glucosidase inhibitors (AGIs)

Alpha-amylase and alpha-glucosidase are the key enzymes responsible for metabolism of carbohydrates [18]. Alpha-glucosidase Inhibitors (AGIs) are oral anti-diabetic drugs preferably for treatment of T2DM. AGIs delay the process of carbohydrate absorption in the gastrointestinal tract by moving the undigested carbohydrate into the

Table 2

Combination therapy of antidiabetic drugs for treatment of T2DM.

Name of the drug combinations	Pharmacological study	Outcome	Reference
Vildagliptin	The study was designed to investigate the relationship of the difference between observed and predicted glycated hemoglobin (dopHbA1c) and the actual HbA1c reduction after the patients were administered with Vildagliptin in T2DM patients.	The investigation of dual therapy of Vildagliptin resulted in a greater reduction in HbA1c in patients with dopHbA1c less than zero.	[152]
Metformin and Sulfonylureas/ acarbose/ thiazolidinedione/ glinides	The assessment was focused on cost effectiveness of metformin based dual therapies along with cardiovascular diseases.	Four metformin based dual therapies were assessed which concluded that the dual therapy of metformin with thiazolidinedione was found most effective with least risk of cardiovascular diseases and was cost effective.	[153]
Metformin & Sulfonylurea with Oral Anti hyperglycemic agent & basal insulin	The study was aimed for the outcomes of triple oral hypoglycaemic therapy compared with basal insulin therapy.	In case of patients receiving basal insulin, major adverse cardiovascular events and hypoglycaemic event were noted in comparison to the patients receiving oral hypoglycaemic agent as add-on therapy.	[154]
Metformin with Sulfonylurea/ anti-hyperglycemic agents	Combination therapy of metformin and sulfonylurea were compared with the combination therapy of metformin and other antihyperglycemic agents in patient with T2DM.	Hypoglycaemic effect of metformin and sulfonylureas combination therapy was associated with high rate of utilization of secondary health care than any other dual therapy of metformin with other oral anti-hyperglycemic agents.	[155]
Metformin with oral hypoglycaemic agents	Fixed dose combination of oral hypoglycaemic agents significantly reduced HbA1c and fasting plasma glucose level thereby reducing hyperglycaemia in patients those who showed failure in monotherapy.	An increased number of randomized trials on the safety and efficacy of newly emerging fixed dose combination suggested the better treatment options for T2DM	[156]
Gliclazide and/or Metformin and/or Acarbose	The effects of Gliclazide, Metformin and Acarbose were studied in monotherapy or in combination therapy on body composition, fat distribution and other risk factors of heart in newly diagnosed T2DM patients.	Blood glucose and HbA1c levels were improved significantly after six months of single drug therapy of metformin. Metformin led to a significant decrease in patient body fat and body fat mass and improvement in levels of serum total cholesterol, triglycerides and adiponectin.	[157]
Metformin with sulfonylurea/ AGIs/ thiazolidinediones/ Glinides/ DPP- IV inhibitors/ SGLT2 inhibitors	Metformin and sulfonylureas were time-tested antihyperglycemic agents which were introduced by other antihyperglycemic agents like glinides, sulfonylureas, thiazolidinediones, DPP- IV inhibitors, SGLT2 inhibitors and AGIs.	The review addressed the advantages and disadvantages of the series of monotherapy and dual therapy of a range of antihyperglycemic agents and their application in monotherapy and combined therapy.	[158]
Alpha glucosidase inhibitors and DPP-IV inhibitors	A triple therapy was conducted with alogliptin (25 mg) in the dual therapy of metformin and sulphonylureas.	The efficacy of the alogliptin was compared with other DPP – IV inhibitors and the safety and cost effectiveness in the dual therapy of metformin and sulfonylurea was found to be better in maintaining the glucose homeostasis, The combination of linagliptin and voglibose was found to reduce bodyweight, improve glycaemic control and reduce plasma insulin significantly as compared to linagliptin alone. The combination of Linagliptin and exendin – 4 had no effect on plasma GLP- 1. The combination of linagliptin and voglibose was more significant in control of glycaemic control than the individual drug therapy.	[159]
GIP and GLP-1	Linagliptin, a DPP – IV inhibitor was tested alone or in combination of voglibose or Exendin – 4 for effect on glycaemic control in T2DM patients.	Linagliptin was able to lower the fasting blood level and HbA1c but very less effect on postprandial glucose level. Linagliptin was more acceptable due to less incidence of hypoglycemia and undesired side effects.	[160]
Alpha glucosidase inhibitor (Voglibose) and Glimepiride or Metformin	In this investigation the effect of Linagliptin monotherapy was compared with mono therapy of voglibose on postprandial blood glucose in T2DM.	Unimolecular dual agonist of GIP/GLP-1 incretins NNC0090-2746 have demonstrated synergistic action in reducing HbA1c, body weight and total cholesterol. The patients on triple therapy showed better glycaemic control on FBS, PPBS and HbA1c. There was significant decrease in BMI and good protective effect on kidney. Voglibose decreased total cholesterol, triglycerides and low density lipoproteins and increased the high density lipoproteins. But there is no change observed in blood urea level in both the groups.	[161]
Alpha glucosidase inhibitor (Voglibose) or Metformin with Insulin	NNC0090-2746 was a fatty acylated unimolecular moiety hybridised GIP/GLP-1 dual agonist, developed clinically for the treatment of T2DM.	Linagliptin was able to lower the fasting blood level and HbA1c but very less effect on postprandial glucose level. Linagliptin was more acceptable due to less incidence of hypoglycemia and undesired side effects.	[162]
Alpha glucosidase inhibitor (Voglibose/ Acarbose) with Metformin and Sulfonylureas	The study included two groups for analyzing the parameters such as BMI, FBS, PPBS, HbA1c, glomerular filtration rate, serum creatinine, blood urea and lipid profile in patients who were administered dual therapy of metformin and glimepiride and the triple therapy of voglibose, metformin and glimepiride.	The patients on triple therapy showed better glycaemic control on FBS, PPBS and HbA1c. There was significant decrease in BMI and good protective effect on kidney. Voglibose decreased total cholesterol, triglycerides and low density lipoproteins and increased the high density lipoproteins. But there is no change observed in blood urea level in both the groups.	[163]
Alpha glucosidase inhibitor (Voglibose) or Metformin with Insulin	Two groups were administered with dual therapy of metformin with Insulin or Voglibose with Insulin.	While comparing the FBS, PPBS, RBS and HbA1c in both the groups, the group of patients on dual therapy of voglibose and insulin received better therapeutic efficacy than the other group treated with metformin and insulin. The reduction in HbA1c was found significant in voglibose with short duration of treatment as compared to acarbose. Both the groups showed reduction in BMI and improvement in lipid profile. Incidence of hypoglycaemia was reduced.	[164]
Alpha glucosidase inhibitor (Voglibose/ Acarbose) with Metformin and Sulfonylureas	In this study, one of the alpha glucosidase inhibitor i.e. voglibose or acarbose was used as add - on therapy to metformin and sulfonylureas.	Action of dapagliflozin in presence or absence of voglibose was investigated and found that the pharmacokinetic was not affected by the presence or absence of voglibose.	[165]
Alpha glucosidase inhibitor with SGLT2 inhibitor (Voglibose with Dapagliflozin)	The investigation was done to assess the effect of oral antidiabetic drugs like voglibose on the pharmacokinetics, safety and tolerability of dapagliflozin in Japanese patients with T2DM.	The hypoglycaemic episodes were reduced on switching from sulfonylureas to mitiglinide/voglibose. There was	[166]
Alpha glucosidase inhibitor with Insulin secretagogues (Voglibose with Mitiglinide)	The combination of mitiglinide with voglibose was chosen for investigation on episodes of hypoglycemia, weight gain and glycaemic control in comparison with sulfonylureas	(continued on next page)	[167]

Table 2 (continued)

Name of the drug combinations	Pharmacological study	Outcome	Reference
Alpha glucosidase inhibitor with Glinides (Miglitol with metiglitinides)	When the second generation alpha glucosidase inhibitor miglitol was combined with glinide (metiglitinides), the change in metabolic profile, incretin secretion and markers for atherosclerosis and oxidative stress were monitored. A novel N-terminal PEGylated amylin analogue, BZ043, was tested for its efficacy as an antidiabetic drug in adjunct with low dose of basal insulin analogue glargin (GLAR).	marked improvement in endothelial dysfunction reducing the microvascular side effects associated with T2DM. The combination of miglitol and metiglitinides was found to be more potent in improving glycaemic control markers. The combination showed reduction in cardiovascular risk factors. The PEGylated analogue implied a 30 fold higher plasma half-life as compared to non-PEGylated peptide. PEGylation not only prevented the self-aggregation property of amylin but also provided a new concept of co-formulation with insulin. BZ043 produced a long lasting control over postprandial hyperglycaemia. In adjunct therapy, the dose of GLAR was reduced to 4 times less than the insulin monotherapy. The HbA1c was improved significantly in the patients after switching the bolus insulin therapy to insulin – liraglutide therapy. The incidence of hospitalization due to severe hypoglycemia was reduced and the body weight reduction was quite significant.	[168]
Amylin analogue with Insulin	This study was carried out for combined therapy of basal insulin with Liraglutide on T2DM patients who had been treated long on basal bolus insulin therapy.	The HbA1c was improved significantly in the patients after switching the bolus insulin therapy to insulin – liraglutide therapy. The incidence of hospitalization due to severe hypoglycemia was reduced and the body weight reduction was quite significant.	[169]
GLP – 1 analogues with Insulin	This study was conducted to note the efficacy and safety of iGlarLixi, a fixed-ratio combination of insulin glargine [iGlar] plus lixisenatide	There was significant reduction in HbA1c in elder patients treated with iGlarLixi. Treatment with iGlarLixi reduced the side effect of insulin and lixisenatide associated weight gain and gastrointestinal side effects. iGlarLixi significantly improved the glycaemic control with less incidence of hypoglycaemic attack. The fixed dose combination was administered as once daily injection, so improved patient compliant.	[170]
Comparison study of two GLP-1 agonists	AWARD 4 was a random, open level phase 3 trial, 52 week study conducted with Dulaglutide versus bed time insulin glargine both in combination with prandial insulin lispro in T2DM patients.	The study for a time period of 52 weeks resulted in significant decrease in HbA1c, weight reduction and lower risk of hypoglycaemia in case of dulaglutide with lispro as compared to glargine.	[171]
DPP – IV inhibitors with Insulin	AWARD 9 was a 28 week study conducted with once a week dulaglutide with titrated insulin glargine in T2DM patients.	Once a week dulaglutide 1.5 mg with titrated insulin glargine improved the glycaemic parameters like HbA1c and showed good weight management with reduction in frequency of injection.	[172]
	The study included insulin glargine/lixinatide in one dosage form containing two subcutaneous antihyperglycemic drug once a day.	Once a day administration of insulin glargine/lixinatide was found to have better glycaemic control in T2DM patients. It overcame the adverse effects of insulin in body weight gain and hypoglycaemia.	[173]
	The study assessed the efficacy and safety of dulaglutide once a week with insulin therapy in T2DM patients who are on haemodialysis	It was found that dulaglutide might improve the glycaemic control reducing the total daily doses of insulin, without increasing the risk of hypoglycaemia, in patients with T2DM treated with insulin who are on haemodialysis.	[174]
	SUSTAIN 10 was a multicenter randomized study carried out at 11 different countries of Europe. The study compared the efficacy and safety of liraglutide 1.2 mg once daily dose with Semaglutide 1.0 mg once a week dose in T2DM patients who were also on 1-3 OAD therapy with different combination therapy of biguanides, sulfonylureas and SGLT2 inhibitors.	The comparative study showed the efficacy of semaglutide was higher than liraglutide in improvement of glycaemic control and reduction of body weight.	[175]
	PIONEER 4 was a random double blind study of oral semaglutide Vs subcutaneous liraglutide.	The comparative study showed the efficacy of semaglutide was higher than liraglutide in improvement of glycaemic control and reduction of body weight.	[176]
	The comparative study of lixisenatide and liraglutide was done to assess the effectiveness and safety in T2DM patients with obesity.	At 26 th and 52 nd week, the oral semaglutide was found to be more efficacious in reducing the weight of subjects as compared to subcutaneous liraglutide and placebo.	[177]
	A retrospective observational study without a control group was carried out with sitagliptin as an add-on therapy to insulin. The efficacy and safety of the dual therapy was assessed.	Significant decrease in HbA1c was observed at 52 nd week in the group treated with oral semaglutide than the subcutaneous liraglutide or placebo.	[178]
	The study was based on evaluation of efficacy, safety and tolerability of vildagliptin / metformin combination on patients with uncontrolled glycaemic parameters treated with insulin.	Two groups treated with lixisenatide and liraglutide showed same reduction of HbA1c and body weight at 24 weeks study.	[179]
	The long term efficacy and safety of vildagliptin add-on therapy with insulin therapy was assessed in patients with T2DM.	Adding sitagliptin to insulin showed similar efficacy and safety in both geriatric and non-geriatric T2DM patients.	[180]
	The efficacy and safety of teneligliptin as add-on to insulin therapy was tested for glycaemic control in T2DM patients with hemodialysis (HD).	Vildagliptin with or without metformin showed significant control on glycaemic parameters and reduction in HbA1c with good tolerability and less incidence of hypoglycaemia.	[181]
		The add-on therapy of vildagliptin to insulin therapy reduced the HbA1c consistently which was observed to be well tolerated. The dose and frequency of dosing or injection of insulin was reduced with decreased risk of hypoglycaemia.	[182]
		Teneligliptin caused improvement of early phase insulin secretion and decrease in inappropriate glucagon secretion. So requirement of post prandial insulin is	[183]

(continued on next page)

Table 2 (continued)

Name of the drug combinations	Pharmacological study	Outcome	Reference
DPP – IV inhibitors with sulfonylureas	The study was done to evaluate and compare the efficacy and safety of glimepiride or sitagliptin with metformin in T2DM patients. VISUAL study was the comparative study of 24 weeks for vildagliptin add-on therapy, increased dose of sulfonylureas (by 50%) in patients with uncontrolled glycaemia with metformin/ sulfonylureas therapy.	reduced so insulin doses needs to be reduced to avoid hypoglycaemia in patients with HD. The glimepiride/metformin showed significant reduction in glycaemic parameters as compared to sitagliptin/ metformin combination. The reduction in FBS, PPBS and HbA1c in vildagliptin add-on therapy group was significant than the increased sulfonylureas dose of metformin/ sulfonylureas group. Vildagliptin add-on group didn't show any evidence of weight gain or hypoglycaemia.	[183]
DPP – IV inhibitors with SGLT 2 inhibitors	The study was based on evaluation of efficacy and safety of co-administration of sitagliptin with ertugliflozin compared with placebo in T2DM patients inadequately controlled on diet and exercise COSMIC study was designed to assess the efficacy and safety of sitagliptin with metformin as initial therapy in T2DM patients.	Co-administration of ertugliflozin/ sitagliptin showed reduction in HbA1c from the baseline. The incidence of urinary tract infection, genital mycotic infection and symptomatic hypoglycaemia were significantly less. The study conducted for four years concluded that sitagliptin/metformin combination can be advised for initial combination therapy in T2DM patients as the reduction of HbA1c was significant. The combination was well tolerated without any serious side effects Vildagliptin / metformin provided greater and durable long term benefits compared to metformin monotherapy in newly diagnosed patients with T2DM. Reduction in HbA1c was consistent with the dual therapy than the monotherapy.	[184]
DPP – IV inhibitors with Biguanide (Metformin)	VERIFY was a random and double blind study carried out for verification of efficacy of vildagliptin / metformin combination as early therapy for T2DM patients.	The study conducted for four years concluded that sitagliptin/metformin combination can be advised for initial combination therapy in T2DM patients as the reduction of HbA1c was significant. The combination was well tolerated without any serious side effects Vildagliptin / metformin provided greater and durable long term benefits compared to metformin monotherapy in newly diagnosed patients with T2DM. Reduction in HbA1c was consistent with the dual therapy than the monotherapy.	[185]
SGLT2 inhibitor with sulfonylureas	The efficacy and safety of the fixed dose combination of alogliptin with metformin was studied in Asian patients with T2DM CANVAS study was done to assess the efficacy of canagliflozin (100 mg and 300 mg) with sulfonylureas in glycaemic and cardiovascular risk control.	The reduction in HbA1c was found to be - 1.53% in fixed dose combination of alogliptin and metformin twice a day as compared to monotherapy and better glycemic control, safety in Asian patients with T2DM. After 52 week study, there was a significant reduction in HbA1c, fasting and post prandial blood glucose, no increase in episodes of hypoglycemia and body weight. Both the doses of canagliflozin showed reduction in systolic blood pressure but no significant reduction was observed in total triglycerides, HDL and LDL cholesterol. Canagliflozin was well tolerated with few reports on mycotic infection in both men and women.	[186]
SGLT2 inhibitor with DPP – IV inhibitors	A retrospective study was conducted to assess the efficacy and safety of a SGLT2 inhibitor i.e. ipragliflozin with a DPP – IV inhibitor sitagliptin.	Ipragliflozin showed significant reduction and control of glycaemic parameters like HbA1c, fasting, postprandial glucose level and body mass index. The study reported that ipragliflozin is more effective in Japanese T2DM patients with hypertension with kidney dysfunction and obesity. The glycaemic control was observed with reduction of HbA1c and fasting blood glucose level at the end of 24 week study. There was no additive or synergistic effect observed in the fixed dose combination. The combination was well tolerated without any safety issues but strictly contraindicated in T2DM patients with renal impairment or hemodialysis.	[187]
SGLT2 inhibitor with biguanides or biguanides plus sulfonylureas	The efficacy and safety of empagliflozin and linagliptin, a fixed dosage combination once a day was assessed in T2DM patients. A meta-analysis study was done to analyze the effect of dapagliflozin along with other antidiabetic drugs. Whether the effect is additive or synergistic effect was assessed in T2DM patients with inadequate glycaemic control.	This meta-analysis indicated that dapagliflozin as an add-on drug to conventional antidiabetic drugs improved the control of the HbA1c and fasting blood glucose levels in T2DM participants. The meta-analysis confirmed a significant reduction in the body weight of T2DM patients was well controlled under treatment of dapagliflozin in combination with other antidiabetic drugs. The study showed significant reduction in HbA1c and body weight for both empagliflozin 10 mg and 25 mg as compared to placebo. The genital infection adverse reaction were more in empagliflozin 10 mg and 25 mg as compared to placebo but well tolerated in elderly patients.	[188]
SGLT2 inhibitor with GLP-1 agonist	The pool analysis was conducted in poorly controlled and obese T2DM patients of more than 65 years with empagliflozin 10 mg and 25 mg add-on to metformin or metformin and sulfonylureas i.e. metformin and pioglitazone. The study included the pharmacokinetic and molecular targets of both metformin and flozins. The combination directs towards the life threatening side effects of both the drugs i.e. metabolic acidosis.	The dual therapy showed improved glycaemic control with lowering of glycated hemoglobin (HbA1c) levels with a low risk of hypoglycemia.	[189]
Comparison of two SGLT2 inhibitors	The study assessed the efficacy and safety of dapagliflozin with GLP-1 agonist liraglutide. The comparative study was conducted with two SGLT2 inhibitors empagliflozin (25 mg/day) and dapagliflozin (10 mg/day).	This was a real world observational 12 month study conducted with or without GLP-1 agonist liraglutide and dapagliflozin. At the end of the study, the reduction in HbA1c, body weight and blood pressure was found to be significant. The study outcomes were measured by reduction in HbA1c, fasting blood sugar level and analysis of cardio-metabolic parameters with safety profile. After 52 weeks, there was significant reduction in HbA1c and fasting sugar in patients treated with other three OADs like metformin, glibenclamide and a DPP-IV inhibitor, which was more in the groups treated with empagliflozin than dapagliflozin.	[190]

(continued on next page)

Table 2 (continued)

Name of the drug combinations	Pharmacological study	Outcome	Reference
PPAR γ agonist with biguanides	The study assessed the efficacy of rosiglitazone as add-on therapy to metformin in T2DM patients	The reduction in cardio-metabolic parameters like blood pressure, body weight and high protein cholesterol level was more significant in empagliflozin than dapagliflozin. There was significant reduction in HbA1c level and fasting blood sugar. In addition, there was significant increase in HDL level but no significant difference was observed for triglyceride, LDL, waist circumference and systolic blood pressure. The dual therapy was well tolerated and effective for treatment of T2DM.	[197]

distal part of small intestine and colon. This class of drugs help in reduction in postprandial hyperglycaemia [56]. AGIs are saccharides that act as competitive inhibitors for the enzymes in the small intestine to slow down the digestion of carbohydrates such as starch, so that glucose from food enters the bloodstream more slowly, leading to the reduction in postprandial hyperglycaemia (Fig. 4). Acarbose obtained from *Actinomyces utahensis* was the first AGIs, used as a competitive moiety for the enzyme alpha glucosidase [57]. Voglibose and Miglitol are the other AGIs used for management of T2DM [58].

These drugs have benefits in reducing post meal blood sugars when usually combined with other diabetic drugs and thus lower HbA1c [59]. They help raise post meal levels of GLP-1 that helps delay digestion and decreased appetite [60]. Side effects of AGIs typically includes bloating, flatulence, gastrointestinal irritation that might be recovered in few weeks [61].

Alpha-glucosidase inhibitors aren't recommended if the person has an inflammatory bowel disease like ulcerative colitis or Crohn's disease, blockage in intestines, digestive disorder in intestines, diabetic ketoacidosis; a condition where body burns fat instead of carbohydrates for energy [61]. Acarbose is not recommended if the patient has an ulcer in large intestine, cirrhosis of the liver and for pregnant women [61,62].

4.2. Amylin analogues

Amylin is a hormone containing a single chain of 37 amino acids. It is co-secreted with insulin from β cells of pancreas [18]. It delays the gastric emptying and suppresses the secretion of glucagon, so maintains both fasting and postprandial glucose level in the blood. It regulates the food intake by modulating the appetite center in the brain [63]. Amylin is deficient in both T1DM and T2DM, so the research and development of amylin analogues were done which maintains the homeostasis of glucose by any one of the following mechanisms

- i) Delaying of gastric emptying
- ii) Prevention of release of glucagon after meal
- iii) Inhibition of food intake and weight gain by controlling the appetite center [64]

Amylin is not suitable as a drug as it aggregates and insoluble in solution form, so chemical analogues were developed which can imitate the action of amylin. Amylin analogues are available in parenteral form used in the treatment of both T1DM and T2DM [64]. The molecules in this type are administered before meals and have similar mode of action as amylin. Pramlintide acetate (brand name - Symlin®) is the available drug in this class of drug and is administered by subcutaneous route of drug administration [64,65].

The most common side effects of amylin analogues are nausea, vomiting, headache and hypoglycemia when taken along insulin. These side effects go away when the patient adjusts himself to the medication [64].

4.3. Incretin mimetics (GLP-1 agonists and DPP-IV inhibitors)

Glucagon-like peptide (GLP) and Glucose dependent Insulinotropic polypeptide (GIP) are the incretins or peptides derived from gut. Incretins are a group of natural metabolic hormones that stimulate a decrease in blood glucose levels [66]. These hormones are released post meal consumption. GLP-1 is a peptide containing 36 amino acids secreted by L cells of gut after introduction of meal. Secretion of GLP-1 is similar to the secretion of insulin from β cells of pancreas [67]. GLP-1 triggers the synthesis and secretion of insulin from β cells of pancreas. Carbohydrate metabolism in L cells of intestine causes closing of ATP sensitive potassium channel and depolarization of membrane leading to entry of calcium ions (Ca^{2+}). This causes secretion of GLP-1 [68]. The half-life of GLP-1 is about 1–2 minutes due to rapid metabolism by dipeptidyl peptide – IV (DPP – IV) enzymes [18]. So the requirement for development of GLP-1 analogues having higher half-life could be one of the way for the treatment of T1DM and T2DM. Again DPP-IV inhibitors also behave like incretin mimetic [69].

GLP-1 agonists or analogues are the new group of injectable for treatment of type 2 DM [70,71,72]. Metabolism of GLP-1 by DPP-IV is due to presence of an alanine residue at the N terminal. Hence the new analogues of GLP-1 were designed by substitution of the alanine group with other amino acids like threonine, glycine and serine [73]. The analogues were more stable *in vitro* to DPP-IV. Different analogues of GLP-1 were not only stable but also twice potent than GLP-1 [73]. Exenatide was the first GLP-1 analogue with glycine residue at N terminal. It was resistant to DPP-IV and has 53% similarity with human GLP-1 [74,75]. It is available with brand names Bydureon®, taken once weekly and Byetta®, taken twice daily. Other GLP-1 analogues are Lixisenatide (brand name - Lyxumia®), taken once daily. Dulaglutide (brand name - Trulicity®), taken once weekly and Liraglutide (brand name - Victoza®), taken once daily [75].

By increasing insulin secretion and inhibiting glucagon release, incretin mimetics have blood glucose-lowering effects which help to reduce HbA1c levels [76]. The side effects of incretin mimetics include diarrhoea, nausea, vomiting, headaches, dizziness, increased sweating, indigestion, constipation and loss of appetite [76].

GLP-1 receptor agonists are recommended as add-on therapy for patients who do not achieve the required limit of HbA1C after 3 months of metformin therapy [77]. GLP-1 receptor agonists are recommended as first-line therapy as an alternative to metformin in patients who cannot tolerate or are contraindicated for metformin therapy. GLP-1 receptor agonists are well suited for early use in T2DM, since they stimulate release of insulin and suppress glucagon secretion only when blood glucose levels are elevated keeping the risk of hypoglycemia low [76] (Fig. 4).

As dual therapy, GLP-1 receptor agonists are recommended in combination with metformin for patients who do not achieve HbA1C goals with only metformin [78]. For patients requiring triple therapy, GLP-1 receptor agonists can be combined with metformin and a sodium–glucose co-transporter 2 (SGLT-2) inhibitor in patients with persistent hyperglycaemia [79]. The triple combination is well suited for

Table 3

Different reports on novel drug delivery of antidiabetic drug delivery for T2DM.

Type of delivery system	Class of drug	Name of drug	Polymer used	Outcome	References
Biguanides	Metformin	Glycerolphosphate– Chitosan Microcomplexation (GP/CH Microcomplex)		2.5 fold longer T_{max} with a 40% improvement in bioavailability were observed with the GP/CH microcomplex of metformin. GP/CH microcomplexes proved as potential carriers for highly water-soluble antihyperglycemic drug, allowing its controlled release and improved oral bioavailability.	[213]
Liposome	Incretin Mimetics	Glucagon-like peptide-1 (GLP-1)	Anionic liposomes Containing DSPEPG8G (10%), DPPC (27%), Cholesterol (36%) and DPPG (27%)	Anionic liposomes conferred maximum entrapment efficiency of GLP-1 which resulted in 1.7 fold enhancement in secretion of insulin and 3.6 times higher serum concentration of GLP – 1 as compared to intravenous administration of GLP – 1 leading to a noticeable antidiabetic medication.	[214]
	Liraglutide		Multivesicular liposomes containing 40 mg/ml soybean phospholipid, 20 mg/ml cholesterol and 25 mg/ml triolein in diethyl ether was mixed with an aqueous buffered solution	Liraglutide in multi-vesicular liposomes was found to be a promising carrier for subcutaneous administration as a lipid depot delivery system. This delivery system was able to lower the glucose level for a prolonged period in T2DM patients as constant therapeutic level of the drug was maintained for about 144 hrs. So it can be designed for once a week subcutaneous dosing regimen for maintaining the glucose level in T2DM patients	[215]
Sulfonylureas	Gliclazide	Span 60, cholesterol		The cholesterol: surfactant ratio in the formulation was found to be responsible for drug entrapment efficiency. Maximum entrapment of the drug was found for cholesterol: surfactant at a ratio of 4:7. Additionally, the formulation showed good oral bioavailability of 89% <i>in vivo</i> .	[216]
Insulin Secretagogues	Repaglinide	Span 60, cholesterol		Niosomes enhanced bioavailability of the entrapped drug	[217]
Niosome	Biguanides	Metformin	Cholesterol, Span 40, Span 60, dicetyl phosphate	The study reported that the niosomal system is an effective carrier with sufficient drug entrapment and prolonged release profile	[218]
			Span 40/cholesterol dicetyl phosphate and DOTAP	The formulation proved to be a promising sustained release system with greater control on hyperglycemic condition	[219]
Insulin Sensitizers – Thiazolidinediones	Pioglitazone		Cholesterol and span 20	<i>In vitro</i> and <i>in vivo</i> studies revealed that the formulation maintained steady drug concentration (sustained effect) for a longer duration of time, thereby enhancing the therapeutic action.	[220]
Insulin Secretagogues	Repaglinide	phosphatidylcholine / Pluronic F127		The physicochemical properties of nanoparticles were affected by different types of surfactant. The mixture of phosphatidylcholine / Pluronic F127 was the best surfactant/ stabilizer	[221]
			Chitosan and gum arabica	Significant reduction in fasting blood glucose level was observed as compared to pure metformin.	[222]
Polymeric Nanoparticles	Biguanides	Metformin	Alginate	The efficacy and potency of metformin loaded alginate nanoparticles were about three times more efficient in reduction in fasting blood glucose level as compared to pure metformin.	[223]
			Eudragit®RSPO and Eudragit®RSPO/PLGA	Burst release of metformin from the nanoparticle was approximately 20% in just 30 minutes whereas 98% of drug was released at 144 hrs in phosphate buffer of pH 6.8	[224]
				Initial burst release of 74–80% was observed followed by a sustained release (92%–100%) in a time period of 12 hrs and 24 hrs for Eudragit®RSPO NPs and Eudragit®RSPO/PLGANPs, respectively	[225]
				The nanosystem was able to cause burst release of metformin within 22 – 24 hrs of	[226]

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Table 3 (continued)

Type of delivery system	Class of drug	Name of drug	Polymer used	Outcome	References
			Chitosan based mesoporous MCM-41 (5.8 nm) and MCM-41–aminopropylsilane (5.93 nm)	administration followed by a sustained release for 15 days.	
			PLGA and Eudragit RS 100	Sustained release of the drug was noted till 24 hrs, with excellent biocompatibility in adenocarcinoma human cell lines.	[227]
			PLGA	8.7% drug release was observed in 1 hr with a comparatively slow release upto 19% within 12 hrs, followed by a sustained release of 91% till 72 hrs.	[228]
	Glipizide		Polycaprolactone	A drop in blood glucose level not more than 25% (in 1 hr) was evidenced, thus lowering the chances of precipitation of hypoglycemia. The levels were maintained for 7 days.	[229]
			Alginate and chitosan	<i>In vitro</i> release showed a burst release followed by a controlled release.	[230]
Sulfonylureas			Eudragit RLPO	Approximately 50% of drug release occurred within 5 hrs, followed by a more sustained release till 24 hrs (~ 80%). Higher AUC _(0–24hrs) of 6460.80 ng h/mL was observed for the nanoformulation as compared to AUC of glimepiride suspension (at an administered dose 2.5 mg/kg/day, orally) of 3172.3 ng h/mL with lesser side effects.	[231]
	Glimepiride		Zein nanoparticle/ PLGA triblock	The zein nanoparticles/ triblock copolymers-based glimepiride was formulated as thermo-responsive <i>in situ</i> gel intramuscular implant. This could deliver the drug in a controlled release manner to maintain the glucose level in diabetic patients. The drug release was 3.3% and 17.3% after 2 and 24 hrs.	[232]
	Glibenclamide		HPMC	Higher drug dissolution (85%) was observed for glibenclamide loaded NPs as compared with pure drug (35%) and commercial preparation (56%) in a time period of 5mins	[233]
Insulin Sensitizers – Thiazolidinediones	Pioglitazone		Poloxamer 188 and Eudragit L 100	97.5% of entrapped drug was released within 60 min with 10 folds enhancement in drug solubility as compared to pure drug. Blood glucose level was noted to be decreased with the nanoformulation when compared with pure repaglinide at a dose of 100 mg/kg, t.i.d. for 7 days. When administered orally, it showed sustained release for 7 days.	[234]
			PLGA and methoxy polyethylene glycol	15% drug was released in 15 hrs with complete drug release in 5 days. The nanoformulation also conferred hemocompatibility.	[235]
Insulin Secretagogues	Repaglinide		Ethyl cellulose and Poly vinyl alcohol	A drastic reduction of 74.3% in blood glucose level was observed in 10 hrs by nanoparticles / polymer mixture when compared to reduction in blood glucose level of 60.8% and 26.9% by multilayer NPs and free drug in a time period of 10 hrs and 4 hrs (10 nmol/kg), respectively when administered subcutaneously	[236]
			Pluronic F-127	The nanoformulation demonstrated an increase in hypoglycaemic effect for 12 hrs as compared to free drug solution	[237]
	Exenatide			administered by subcutaneous administration at a dose of 10 mg/kg. Higher gastric residence time (24 hrs) was observed when compared with unmodified NPs (10 hrs).	
Incretin Mimetics			Fc modified polyethylene glycol-poly lactic-co-glycolic acid	Encapsulation of liraglutide in PLGA nanoparticle not only prevented the degradation of the drug by the intestinal enzymes but also increased the intestinal epithelial permeability and thereby enhanced the bioavailability and efficacy of liraglutide administered orally.	[238]
	Liraglutide		poly (lactic-co-glycolic acid) [PLGA] nanoparticles		[239]

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Table 3 (continued)

Type of delivery system	Class of drug	Name of drug	Polymer used	Outcome	References
Nanoemulsion	Insulin Secretagogues	Repaglinide	(polylactide acid)-[PLA] nanoparticle coated with a cyclic, polyarginine-rich, cell penetrating peptide (cyclic R9-CPP)	This formulation resulted in high therapeutic efficiency with 4-5-fold increase in oral bioavailability of liraglutide.	[240]
			Span 80, Tween 80, olive oil and acetone	AUC of 49.58 mg h/mL, with C_{max} of 11.12 mg/mL and T_{max} of 4 hrs was observed for the nanoemulsion.	[241]
			Sefsol-218, Tween 80 and Transcutol	A dose of 1 mg/kg was able to reduce the blood glucose level by a maximum of 67%.	[242]
			Labrafac PG, Tween 80, and propylene glycol	Improved dissolution rate with higher % of drug release was observed for the nanoformulation when compared to pure drug.	[243]
	Insulin Sensitizers – Thiazolidinediones	Pioglitazone	Capryol 90, Transcutol HP, Cremophor ELP	The formulation displayed a 60% drug release in a time period of 24 hrs, while a 17% and 10% of drug release was observed for marketed preparation and pure drug, respectively.	[244]
			Capmul MCM C8, oleic acid, Cremophor RH 40, Tween 80, Transcutol P	A complete drug release from SMEDDS was observed in 40 min, in contrast to 26% and 38% from pure drug and marketed preparation (Actos Tablet, 15 mg), respectively. The drug release was found to be pH independent.	[245]
			Glipizide	Improved bioavailability was displayed by the nanoformulation with a marked reduction in blood glucose level as compared with pure drug suspension at an administered dose of 800 mg/kg, i.g. Increased AUC (0–24hrs) of 248.88 ± 52.22 and 234.64 ± 32.22 was noted for free drug suspension (L - SNEDDS) and solid state SNEDDS(S-SNEDDS), respectively. The AUC (0–24hrs) of pure drug and marketed formulation was found to be 128.77 ± 54.25 and 207.20 ± 34.16 , respectively at a dose of 1 mg/kg, orally. More than 90% of glibenclamide was released in 5 min. by the nanoformulation at a pH of 1.2 and 7.4 while less than 10% drug was found to be released in 30 min. by the commercial formulation and pure drug. All the formulations displayed pH independent drug release.	[246]
	Self nano-emulsifying drug delivery systems	Glimepiride	Miglyol_ 821, Tween 80, PEG 400, aerosol 200	Rapid onset of action was observed in a time period of 1 hr with sustained effect till 8 hrs. 30% and 50% of repaglinide got released within 2 hrs by RG-SLN1 and RG-SLN2, respectively. RG-SLN1 portrayed sustained effect till 12 hrs, as compared to 8 hrs by RG-SLN2.	[247]
			Glibenclamide	Precirol and lecithin	[248]
	Insulin Secretagogues	Repaglinide	Stearic acid, Pluronic F68 and soya lecithin	Lipohydrogel nanoparticles (LHNs) entrapping repaglinide were prepared by coating chitosan on SLNs. Reduced burst release was seen for repaglinide loaded lipohydrogel nanoparticles (LHN) when compared with SLN and free drug solution. Reduced toxicity was also observed with the formulation when compared with SLN. Prolonged drug release was observed. The nanotubes maintained hypoglycemia for a much longer time period.	[249]
			Chitosan	Nanocrystal of gliclazide had improved solubility, dissolution and bioavailability. The formulation showed initial faster release followed by delayed release facilitating the delivery of gliclazide to maintain the glucose homeostasis in T2DM patients with better therapeutic activity. Sustained release of metformin was observed till 10 hrs with high drug entrapment efficiency	[250]
Carbon Nanotubes	Biguanides	Metformin	(D, L-lactide-coglycolide) [PLGA] second generation nanocrystal, 0.5% w/v poloxamer -188	Sustained release of metformin was observed till 48 hrs with enhanced drug permeation.	[251]
Nanocrystal	Sulfonylureas	Gliclazide	Soya Lecithin, Span 60 and Span 40	[252]	
Nanoformulations in Transdermal patches (TDPs)	Biguanides	Metformin	propylene glycol, Polymethacrylic acid and soya Lecithin	[253]	
	Sulfonylureas	Glimepiride		[254]	

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Table 3 (continued)

Type of delivery system	Class of drug	Name of drug	Polymer used	Outcome	References
Insulin Secretagogues	Repaglinide	Cephalin, lecithin and Tween 80	Chitosan, HPMC, Oleic acid, Tween 80, DMSO	HPMC SNEDDs entrapping glimepiride displayed increased AUC (0–24hrs) of 29501.1 ng h/mL when administered orally. Improved skin permeation with higher permeation with significant glucose lowering effect by HPMC films was observed as compared to chitosan films. Sustained drug release was observed till 48 hrs with no event of severe hypoglycemia.	[257]

overweight patients. Additionally, incretin use with basal insulin may delay the use of mealtime insulin with reduced risk of hypoglycemia [79, 80]. This simplified regimen reduces the need for matching mealtime insulin to specific carbohydrate ratios and also helps mitigate the weight gain with insulin use [80].

Dipeptidyl peptidase - IV (DPP-IV) is a serine protease, which is present in membrane bound form and plasma soluble form [81]. The enzyme is responsible for degradation of number of biologically important peptides. DPP-IV deactivates GLP-1, so the DPP-IV inhibitors increases the activity of GLP-1. Inactivation of DPP-IV causes the increase in half-life of GLP-1 (Fig. 5). Most of the DPP-IV inhibitors are peptide derivatives of α- amino acyl pyrrolidines [82]. Currently following DPP-IV inhibitors are available in the market due to high oral bioavailability like Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, Alogliptin, Gemigliptin, Anagliptin, Teneligliptin, Alogliptin, Trelagliptin and Omarigliptin [83].

4.4. Sodium glucose co-transporter 2 antagonists/ inhibitors

Reabsorption of glucose in proximal convoluted tubule (PCT) is achieved by passive transporter, facilitative glucose transporter (GLUT) and active co-transporter, sodium glucose co-transporter (SGLT) [84]. SGLT2 inhibitors inhibit the SGLT2 present in PCT which prevents reabsorption of glucose and enhances the excretion of glucose in urine (Fig. 6). As glucose is excreted in urine, the glucose level in the blood is maintained and other glycaemic parameters are maintained [85]. The available molecules in this category are Canagliflozin, Dapagliflozin, Empagliflozin, Ipragliflozin, Luseogliflozin and Tofogliflozin [86]. SGLT2 inhibitors are used in monotherapy or in combination with metformin, sulfonylurea or thiazolidinediones or as add on with insulin [87].

5. Monotherapy for the treatment of T2DM

Monotherapy for the treatment of T2DM is targeted for reduction of glycosylated hemoglobin (HbA1c) up to 0.5 to 1.5% [88]. Further control of postprandial glucose level becomes more pertinent for improvement of HbA1c when the value meets the recommended value of less than 7% [89]. Metformin is the drug of choice for first line treatment. In conditions where metformin is contraindicated in certain patients or the patients experience associated complications on metformin use, use of other available hypoglycemic agents is chosen as first line treatment for the said disease condition [89,90]. The details of the drugs that are appropriate for the treatment of T2DM are entailed in Table 1.

5. Combination therapy for treatment of T2DM

When the monotherapy fails to control the glycemic parameters in the treated patients, combination therapy is recommended to the patient to achieve the glycemic control and thereby delay the deterioration of β - cells. Combination therapy may be dual or triple drug combination

therapy. At times oral hypoglycaemics are also combined with insulin therapy [145,146]. Initial combination therapy for a T2DM patient requires some considerations like

- Whether the combination therapy would be effective in reduction of clinical intensification of diabetes, as the maintenance of glycemic control becomes harder for the patient with the aid of diet and exercise regimen [147].
- Whether the combination of different medications would cause improvement of diabetic conditions by modification of β - cell function. The combination therapy may improve the pathophysiology of diabetes [148]
- Whether the combination therapy would be patient compliant according to acceptance, dosing frequency and safety [149]
- Cost of the combination therapy is another prime factor for the affordability by the patient [150]
- Whether the risk-to-benefit ratio is acceptable [151]
- Combination therapy may be helpful as per the assessment of primary and secondary end points. Whether it is able to overcome the problems associated with single therapy of add-on of insulin which causes weight gain and hypoglycemia [145]

Some of the studies involving combination of different drugs studied for the treatment of T2DM are illustrated in Table 2.

7. Novel drug delivery system for antidiabetic drugs for T2DM

Conventional drug delivery systems have certain limitations like lack of efficacy due to improper or ineffective dosage, decreased potency or changed effects due to drug metabolism and lack of target specificity [198,199]. Novel Drug Delivery systems (NDDSs) is one of the emerging field in recent years due to their benefits in reduced dosing frequency, enhanced bioavailability, prevention from degradation in acidic gastric environment, targeted therapeutic efficacy with decrease in associated side effects [200]. Though numerous NDDSs are researched upon for treating various diseases, few are reported for treatment of T2DM. These can be classified as:

1. Particulate system – i) Microparticulate system ii) Nanoparticulate system
2. Vesicular system - i) Liposomes ii) Niosomes
3. Others - i) Self nano-emulsifying drug delivery system (SNEDDS) ii) Transdermal drug delivery system

The particulate system consists of miniaturized structures which can provide intracellular drug transport and coupling of ligands makes them recognized by the specific receptors. These systems are therefore perceived to be the most desirable carriers for the delivery of anti-diabetic drugs [8].

Microparticle-based therapy enables the targeted release of entrapped drugs at the targeted site. These systems maintain the drug concentration in plasma by manipulating its release rate. As microparticles are smaller in size, they have larger surface to volume ratio which is utilized for enhancement of dissolution of insoluble drugs [201]. The

mechanism of transport of microparticulate systems is transcellular transport through carrier or receptor mediated endocytosis. Due to the size, microparticles cannot enter into the cells by paracellular transport as they cannot cross the tight junctions of mucosal membrane whereas nanoparticulate systems have higher intracellular uptake as compared to microparticulate system [202]. The nanoparticles are categorized as polymeric nanoparticles (NPs), metallic NPs, lipid based NPs and biological NPs [203]. Nanoparticles deliver the entrapped drugs by both cellular uptake process such as transcellular and paracellular pathway [204]. Apart from this, the NPs portrays increased mucoadhesion as they are retained in the gastrointestinal tract by electrostatic interaction between positively charged NPs and the negatively charged mucus and endothelial layer. At times, the NPs are physically captured by the mucus layer [203].

Because of the proximity to lipid bilayer like architecture of the cell membrane, vesicular systems are foreseen to have substantial potential in drug delivery applications [205]. The vesicular systems are known to be safe and has the ability to maintain drug concentration in the biological system for a relatively longer time duration by controlled release pattern [200]. These carriers are endowed with advantages of improving the stability in the circulation, maintaining therapeutic dose in plasma with the ability to reduce dose dependent toxicity. Liposomes can be unilamellar (ULV) or multi lamellar vesicular system (MLV) [206]. Various formulation strategies are being developed to administer the drug for prolonged period, increased drug loading efficiency and triggered release of the formulation at the required site of action [207]. Niosomes are the vesicular system having lamellar structure containing non-ionic surfactant which are self-assembled. These carrier systems are developed to improve the oral bioavailability of poorly water soluble drugs, reduce the frequency of dosing and dose dependent toxicity of drugs with lower half-life. Niosomes improve the oral bioavailability of poorly water soluble drugs by delivering the drugs at the desired site of action and controlling the release pattern in a controlled manner for a prolonged duration [208].

The self nano-emulsifying drug delivery system (SNEDDS) can be defined as an anhydrous homogenous liquid mixture containing oil, surfactant, drug and co-emulsifier or solubilizer. It is an oil-in water nano-emulsion liquid form which encapsulate the insoluble drugs of BCS class II and IV in dissolved form of particle size in 200 nm or less [209]. It improves solubility of drugs, provides large interfacial area for increased rate of absorption of insoluble drugs. SNEDDS provide better enzymatic and chemical stability and enhances oral bioavailability of insoluble drugs [210,211].

Transdermal delivery system (TDS) follows an alternative mode of administration for drugs other than the oral and parenteral route. TDS is inexpensive, non-invasive, self-administrable and patient compliant. The problem of premature metabolism of drug by first pass metabolism can be overcome by TDS [200]. TDS can be an option for delivery of hydrophilic drugs, macromolecules and vaccines with the use of permeation enhancers [212]. Different reports on novel drug delivery of antidiabetic drug delivery is illustrated in Table 3.

8. 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 nanoformulation 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 nanoformulations 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.

Declaration of Competing Interest

The authors report no declarations of interest.

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