ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Diabetes Mellitus: An overview of conventional therapy and different Drug Delivery Technology.

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder, which is enhanced the blood glucose level and lead to various complications. In current era Insulin, insulin preparation, oral hypoglycemic and genetic drugs are use for the treatment of diabetes mellitus. However, there is still no complete therapy strategy for diabetes mellitus management by far due to limits in administration routes and adverse effects caused by long-term injection of insulin and its preparation and various oral preparations lead enzymatic degradation, chemical instability and poor gastrointestinal absorption. Therefore, it is an urgent need to design suitable delivery systems and explore complete therapy strategies according to the characters of drugs and diabetes mellitus. Appropriate drug delivery systems may enhance the drugs stability, increase bioavailability, and mimic endogenous insulin delivery and reduce the risk of hypoglycemia. This review aims to provide an overview related with the research advances, development trend of drug therapy and the application of delivery systems in the treatment diabetes mellitus, which could offer reference for the application of various drugs in the field of diabetes mellitus treatment.

Keywords: Diabetes Mellitus, Drug delivery, Insulin, Gene therapy, Hypoglycemia.

https://doi.org/10.33887/rjpbcs/2025.16.3.12

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ISSN: 0975-8585

INTRODUCTION

In current era, the occurrence of diabetes mellitus (DM) has increased worldwide. As per the International Diabetes Federation (IDF), by 2030 about 643 million people will we projected with diabetes and these cases will rise to 783 million by 2025 [1]. Diabetes affects estimated 537 million adults of worldwide.

After the cardiovascular disease and cancer DM has become a third most severe non-communicable disease that causes high mortality and morbidity. DM is an endocrine and metabolic disorder which enhanced blood glucose level. It is mainly caused by genetic, environmental influence, microbial infection, and immune dysfunction that cause inadequate insulin secretion and insulin resistance. Untreated chronic DM will affect others and cause diabetic retinopathy [2], diabetic nephropathy [3] and diabetic hypertension [4]. Acute DM will lead to diabetic ketoacidosis and hyperglycemia [5]. Hence, DM has become a vital health problem. World Health Organization (WHO) classified DM into type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes, and special types of diabetes. T1DM, also known as autoimmune diabetes, is characterized by insulin absolutely deficiency due to the damaged pancreatic b-cell function.

The T1DM is caused by a combination of polygenic and environmental factors. Most of these genetic factors are associated with autoimmunity, such as HLA, PTPN22, CTLA-4, and IL2RA [6]. It has been reported that HLA on chromosome 6 is the major genetic risk factors among them. INS polymorphisms influence the processes of thymic immune tolerance and protect against T1DM development by regulating the expression and metabolism of insulin [7]. In patients with T1DM, anti-gen presenting cells wrongly produce specific antibodies against pancreatic b-cells that destroy the ability of pancreatic b-cells and to synthesize and secrete insulin. The oxidative stress plays a pivotal role in the failure of the main glucose regulatory mechanism. The secretion and action of insulin are controlled by insulin signaling cascade, hyperglycemia-induced oxidative stress that damages pancreatic cells. Three kinds of cytokines such as IL-b, TNF-a, and IFN-g involves in apoptosis of pancreatic b-cells of T1DM patients [8]. Therefore, the treatment of T1DM should focus on reconstructing the immune tolerance of pancreatic b-cell and protecting the function of it.

T2DM is non-insulin dependent diabetes that involves insulin resistance, impaired pancreatic b-cells function, obesity, oxidative stress [9] and genetic susceptibility. Because of irregular metabolic process the efficiency of insulin-mediated glucose uptake and utilization by skeletal muscle, adipocyte and liver decreases. To maintain normal blood glucose levels pancreatic b-cells secrete excessive insulin which causes hyperinsulinemia. This excessive amount of insulin in plasma causes less sensitivity of target cells to it, which leads to the depletion of pancreatic b-cells and insufficient synthesis and secretion of insulin [10]. These changes further aggravate insulin resistance that is the main cause of T2DM. Hence, the treatment of T2DM should focus on increasing the sensitivity of target cells to insulin and protecting pancreatic b-cell. The pathogenesis of DM shown that pancreatic b-cell plays a significant role in the DM.

Conventional targets in diabetes

Conventional targets are use for long time for the treatment of diabetes but they have several disadvantages like weight gain, hypoglycemia. These targets only manage the diabetes and delay its complications.

The Biguanides target maintained blood glucose levels decreases glucose output and increases glucose utilization in skeletal muscles and liver. SGLT-2 target boost the glucose excretion from the kidney. Alpha-Glucosidase inhibitors decrease the glucose and free fatty acids absorption from intestine. Sulphonyl urea target increases the insulin release and sensititvity from pancreas. 2,4-thiazolidinediones decreases the secretion of FFA from the fat's cells (**Figure 1**). Researchers working on the receptor target for the designing of newer diabetic therapeutics. Various in-silico, in-vitro, in-vivo and clinical studies have been performed by targeting receptors.

ISSN: 0975-8585

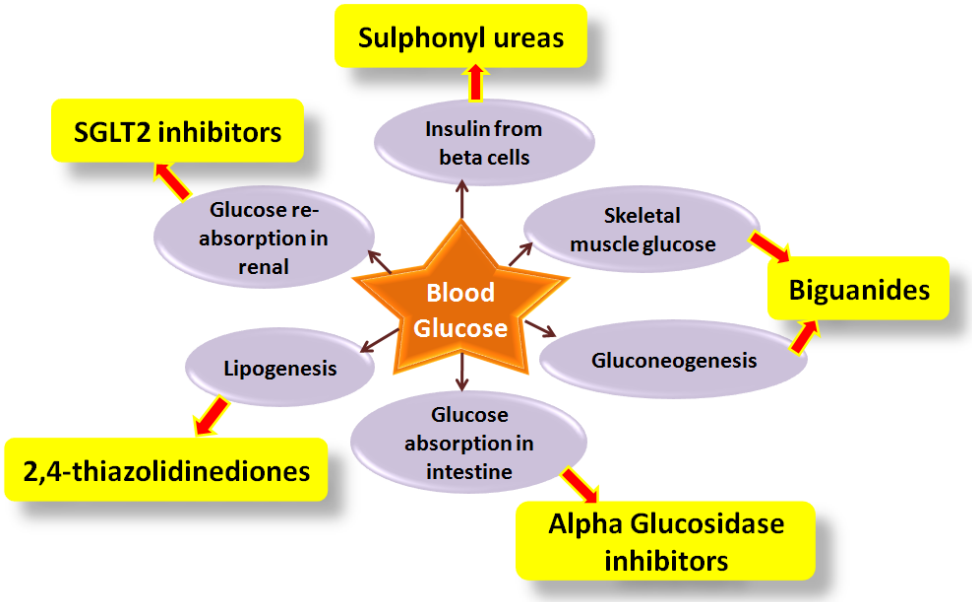

Figure 1: Conventional therapy in DM.

Peroxisome proliferator-activated receptors (PPAR)

PPAR receptor plays an important role in metabolism of free fatty acids, cholesterol and lipids which improve the insulin sensitivity to body [11]. PPARs are subdivide into three types PPARα, PPAR-γ, and PPARβ/δ which act as the transcription factors that regulate gene expression [12]. Thiazolidinediones derivatives act as agonists on PPAR- γ receptor and improve insulin sensitivity in the body (**Figure 2**) [13].

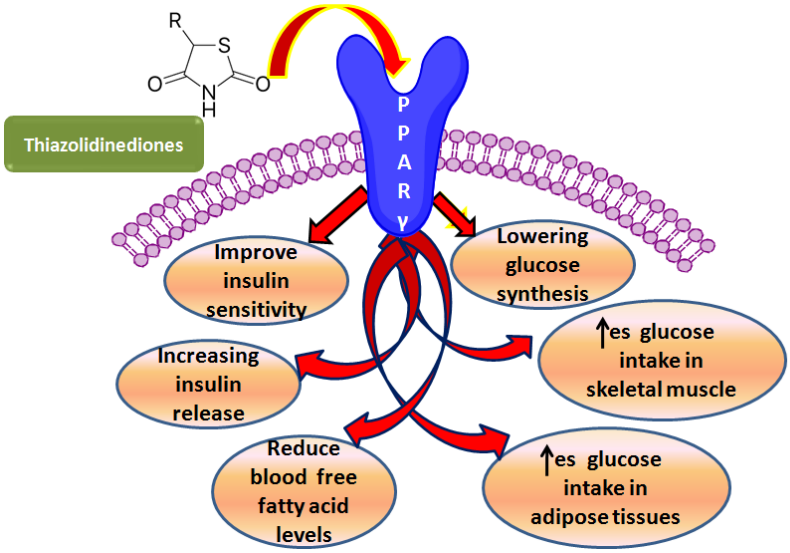

Figure 2: Mechanism of action of Peroxisome proliferator-activated receptors

Glucose-dependent insulinotropic polypeptide (GIP)

GIP hormone is present in the β-cells, adipose tissue and in brain that's helps to regulate blood sugar levels and food intake. GIP also plays an important role in T2DM by boosting the insulin response and raising the secretion of insulin which is triggered by the post-prandial rise in glycemia [14].

G-Protein coupled receptor (GPCR 119)

GPR119 is a G-protein coupled receptor of Class-I which is present in the muscles, liver along with the β-cells of the pancreas [15]. In pancreas its activation enhances the insulin production and its secretion by improving the glucose homeostasis, and releasing the release of GLP-1 and GIP in enteroendocrine cells [16].

Free fatty receptor-1 (FFA 1)

FFA1 is a Class-A G-protein coupled receptor, also known as G- protein coupled receptor-40. It is present in pancreatic and intestinal cells also found in the taste buds and central nervous system [17]. Alquier T, et al. 2009 has reported the role of FFA1 in lipid and glucose metabolism which enhance the secretion of insulin from pancreas [18].

Melatonin

Melatonin hormone is released at night from the pineal gland. Melatonin plays an important role in diabetes management by regulating insulin release from pancreas and regulating glucose level [19]. Melatonin 1 (MT1) and MT2 receptors are present at the extracellular membrane of several cells of body. Mühlbauer E, et al. 2009 has reported that the MT1 receptor increased insulin resistance and glucose tolerance in mouse that indicates the importance of MT1 receptor for maintaining blood glucose level in the body [20, 21]. Reutrakul S, et al. 2018 has reported the clinical studies of melatonin for the treatment of diabetic by lowering the melatonin concentration in circulation [22].

Future targets

Molecular pathway of diabetes are not fully understood, researchers are finding newer targets for the regulation of insulin release and glucose metabolism. In this continuation the development of newer lead molecules are required. Some targets also unknown but they have role in diabetes management shown in Table 1.

Table 1: Future Targets for Diabetes management

Targets	Class	Mode of action	Potential role in diabetes	Ref.
11β Hydroxysteroid dehydrogenase	Glucocorticoids	High levels cause glucose intolerance By inhibiting 11β-HSD Decrease in blood glucose levels	Improved insulin sensitivity	[23]
ACRP-30	Hormone	Low levels cause insulin sensitivity	Increase in Acrp30 will increase the insulin sensitivity and decrease in blood glucose levels	[24]
FETUIN-A	Glycoprotein	Involved in the inflammation of the β-cells	Low levels of Fetuin-A will increase the insulin sensitivity	[25]
VISFATIN	Protein	Attaches to the insulin receptor	Insulin-mimetic action	[26]
METRNL	Adipokine	Cause up regulation of the PPARγ pathway	Increase in the insulin sensitivity	[27, 28]
PEDF (Pigment epithelium-derived factor)	Glycoprotein	Increase kinase-mediated Serine/ Threonine phosphorylation cascade of IRS which causes insulin resistance	Decreasing level of PEDF increases the insulin sensitivity	[29]

VASPIN (SERPIN A12)	Serum glycoprotein	Vaspin performs its action by inhibiting the KLK7	Due to inhibition of KLK7, insulin signalling is improved and also the half-life of insulin is increased that helps in decreasing the blood glucose levels	[30]
GPER (G protein-coupled estrogen receptor)	Glycoprotein	Regulation of glucose homeostasis by binding to both Gi/o and Gs proteins	Increase insulin secretion	[31]
GENE THERAPY	Gene	Act by correcting or repairing the defective genes	Suppression of auto reactive T cells to stop islet cells destruction	[32]

Drug Therapy

The pathogenesis of DM is more complicated, therefore therapeutic management of DM involves diet management, exercise, glucose monitoring, and mood assessment, along with medicines. Insulin, insulin analogs, and non-insulin hypoglycemic drugs, insulin secretagogues and glucose regulators and gene therapy are the medication use for the treatment of DM.

Insulin and its preparations

Table 2: Different analogs of Insulin

Type	MOA	Preparations	Remark	Ref.
Rapid-acting analogs	Accelerate insulin absorption. Lower the risk of hypoglycemia by maintaining insulin concentrations for longer time	Insulin lispro (Humalog), Insulin glulisine (Apidra), Insulin aspart (NovoLog)	Suitable for patients with postprandial hyperglycemia. Injected 0–15 min before or immediately after meal	[34]
Long acting analogs	It establishes a healthy baseline blood sugar level. When food enters the body, blood glucose will increase from a lower and more regular point, making it easier to manage.	Detemir, glargine and degludec	Use for the patients with supplementary therapy. Electronic insulin pump to deliver long-acting insulin	
Premix insulins	Composed of quick-acting insulin analogs and protamine crystallized insulin analogs. Control the fluctuation of blood glucose after 2 h of the meal	Premixed aspartate insulin 30, premixed aspartate insulin 50 and premixed lysine insulin 25	Regulate the level of fasting blood glucose	[35]

When insulin release reduces in patients with T1DM and T2DM, insulin and is analogues are the main exogenous drugs for the managment of DM. Insulin and its analogues regulate the metabolism of sugar, fat and protein and maintain normal blood glucose levels. Insulin also stimulates the receptor of muscle and adipose tissue and help to accelerate glycogen synthesis and inhibit its breakdown [33].

Insulin is a polypeptide compound; therefore, it has several disadvantages such as poor stability and rapid metabolism in vivo limited the application of human insulin in clinic. Hence, various human insulin analogs were synthesized by genetic engineering technology by modification of amino acid sequence. These analogues simulate the metabolic process of endogenous insulin in vivo more accurately and meet the physiological needs of humans. Insulin analogs are classifying into three categories showed in Table 2.

Non-insulin Hypoglycemic agents

Non-insulin hypoglycaemic agents are the first line drug for the treatment of diabetes and management of normal blood glucose level. It also involves diet management and exercise. These drugs are sub classified into biguanide, sulfonylurea, thiazolidinedione, glinide, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists and sodium-glucose cotransport protein 2 inhibitors. Currently researchers are focusing on free fatty acid receptor 1 agonists, glucokinase agonists and protein tyrosine phosphatase-1B inhibitors for the development of potent anti-diabetic therapeutics. Based on the mechanism of action these drugs are classified into insulin sensitizers, insulin secretagogues and glucose regulators.

Insulin Sensitizers

Adenosine 50-monophosphate activated protein kinase (AMPK) is a serine/threonine kinase that is ubiquitously expressed in various tissues and cells, such as brain, heart, liver and skeletal muscles. As an intracellular fuel-sensing enzyme, it is involved in bonding the energy sensing to the metabolic manipulation and also contributes to better energy balance in cells. AMPK is activated by correlative upstream kinases and is able to promote the glucose uptake and the oxidative metabolism of lipids in skeletal muscles and liver, and suppress the glycogenesis in liver and lipid synthesis. It has a strong effect on cell energy metabolism and ameliorates insulin resistance. Considering its pivotal role in controlling energy homeostasis, AMPK has attracted widespread attention as a potential therapeutic target for metabolic diseases, especially for T2DM [36].

Insulin Secretagogues

Free fatty acid receptor-1 (FFAR-1), also known as G proteincoupled receptor 40 (GPR40). FFAR1 is strongly expressed in pancreatic b-cells and enteroendocrine cells of the gastrointestinal tract. When blood glucose levels increase the binding of free fatty acids to GPR40 receptor stimulates glucose-dependent insulin secretion [37]. FFAR-1 could not only directly stimulate insulin secretion from pancreatic b-cells, but also act on the enteroendocrine cells of the gastrointestinal tract. Its activation stimulates incretins secretion, activates GLP-1 receptors and indirectly promotes insulin secretion [38]. The glucose-dependent secretion of insulin reduces the probability of hypoglycemia, which makes GPR40 an excellent target for developing therapies that could be efficacious with fewer side effects. GPR40 agonists are mainly divided into four categories: thiazolyl derivatives, phenoxyacetamide derivatives, propionic acid derivatives, and pyrrolyl analogs. It has reported that the drugs under the research are including JTT-851 in clinical Phase II, P-11187 and LY-2881835, which are all in clinical Phase I [39].

Glucose Regulators

Sodium-glucose cotransporter 2 (SGLT2) inhibitor is novel class of hypoglycemic drugs that promoting insulin secretion. Sodium–glucose cotransporters 1 (SGLT1) and SGLT2 are mediators of epithelial glucose transport. SGLT1 involve in dietary glucose uptake in the intestine, SGLT2 is responsible for glucose reuptake in the tubular system of the kidney. In healthy condition about 180 g per day glucose is filtered from the urine and then almost all of it is reabsorbed by the proximal tubules, 97% is mediated by SGLT2 and 3% is mediated by SGLT 1 [40]. But in diabetes patients the enhancement of glucose reabsorption in the renal tubules would make the blood glucose concentration for much worse. Therefore, SGLT2 inhibitors competitively bind glucose with transporters and inhibit renal tubular reabsorption of glucose, and assist excess glucose to be excreted with urine to regain euglycemia. At the same time, the inhibitors do not act on pancreatic cells or intestinal cells to aggravate the burden of insulin secretion, which plays a protective role in

the function of pancreatic b-cells. SGLT-2 inhibitors also have some adverse reactions, mainly including ketoacidosis, hypoglycemia and urogenital system infection. Ex of SGLT-2 inhibitors include daglitazone, englenet, ruglietin, caglione, eglitoglione, etc [41].

Gene Therapy

From the literature is it has been observed that the diabetes treatments from insulin, insulin analogs and noninsulin hypoglycemic drugs that temporarily minimize the symptoms of hypoglycaemia but could not permanently improve the function of islet cells, maintain blood glucose homeostasis, and avoid various complications. The mechanism pathway of exogenous insulin systemically is quite different from the secreted insulin from the endocrine pancreatic b-cells. Gene therapy involves transfer of exogenous genes into appropriate recipient cells in diabetes patients for therapeutics action [42]. Gene therapies mainly target the root cause of diseases and enable us to arrest or reverse a condition. The main genetic drugs used in gene therapy include DNA, small interfering RNA (siRNA), mRNA, microRNA or antisense oligonucleotides. The gene therapy for diabetes mellitus could be divided into replacement gene therapy, immune gene therapy and regulatory gene therapy.

Replacement Gene Therapy

In T1DM and T2DM different degrees of damage has been found in the pancreatic cells. This damage is replaced by constructed non-beta-cells that redressing the deficiency of insulin synthesis and secretion. The replacement gene therapy has several advantages [43]: (1) effective insulin gene transfer; (2) control the expression and release of insulin; (3) transfected cells produce proinsulin into mature and active insulin; (4) target cells with biochemical properties similar to b-cells but not be attacked by the immune systems.

Viral vectors such as lentivirus and adeno-associated virus, and non-viral vectors such as liposomes and plasmids have been utilized to deliver genes into target tissues or cells, such as pancreas, liver, intestinal endocrine K cells and muscle cells. Among them, intestinal endocrine K cells, which have many similarities with pancreatic b-cells, could produce glucose-dependent insulinotropic polypeptide (GIP) and contain prohormone converting enzymes essential for proinsulin processing [44].

Tuduri et al., 2012 has reported that transgenic mice diabetes induced by streptozotocin (STZ), after transferring the GIP promoter into K cells of the gastrointestinal tract area, showed long term euglycemia [45] and produce sufficient amount of insulin to maintain glucose homeostasis. Romer and Sussel et al., 2015 introduced adeno-associated viral vectors carrying insulin and glucokinase genes into the skeletal muscle of STZ-induced diabetic mice and dogs [46]. The co-expression of these two genes enhanced the translocation of GLUT4 and glucokinase, and elevated glucose transport into muscle cells.

Immune Gene Therapy (IGT)

Immune gene therapy is mainly used for T1DM patients. IGT blocks or reverses the process of autoimmune response by transducing target genes and protect the function of islet cells of pancreas and reduce the reliance of the patient on insulin administration.

The anti-inflammatory cytokine interleukin 10 (IL-10) changes the immune response of the organism and the expression of MHC class II antigens. It has been reported that intramuscular recombinant adeno-associated viral vector encoding murine IL-10 (rAAVIL-10) was injected into nonobese diabetic mice.

Regulatory Gene Therapy

For the generation and maturation of pancreatic b-cells various cytokines are involve that regulate the synthesis and secretion of insulin. Researchers are working to transfer the genes encoding interrelated cytokines into the organism to facilitate the normal secretion of insulin and maintain blood glucose homeostasis.

Insulin-like growth factor 1 (IGF1) is a beta-cell mitogen which could enhance the absorption of glucose and amino acids, promote the synthesis of glycogen, and improve the sensitivity of organs to insulin. IGF1 overexpressing in b-cells arrested the overexpression of human interferon-b (IFN-b) in b-cells which prevented the islet infiltration and immune cell-mediated b-cell death in transgenic mice [47].

Mallol et al. 2017 has prepared and injected the AAV8-IGF1-dmiRT, encoding IGF-1 into the pancreatic alveolar cells of adult mice to achieve tissue-specific gene expression. The results revealed that the expression of IGF1 in pancreas prevent the onset of diabetes in non-obese mice by blocking b-cell directed autoimmune attack [48].

Application of Drug Delivery Systems in Diabetes Mellitus Treatments

Due to the challenges of diabetes treatment and advantages of nanoparticles (NPs) in drug delivery [49], researches are working on nano-carriers for the treatment and management of diabetes mellitus.

Nanoliposome

Liposomes are spherical vesicles composed of lipid bilayers of phospholipids. Liposome are suitable for encapsulation of both hydrophilic and hydrophobic drugs [50]. Liposomes are attractive target for diabetes drug delivery due to its biocompatibility, biodegradability, poor immunogenicity, protective effect against enzymatic degradation and cell-specific targeting.

Cho et al., 2019 has injected lecithin liposome Cas9-RNP complexes in T2DM mice that remarkably downregulate dipeptidyl peptidase-4 gene (DPP-4), accompanied by euglycemia, insulin response, and alleviated liver and kidney damage [51].

Polymer Nanosphere

Polymeric nanospheres are micron size spherical solid particles that are composed of polymers. Rodriguez-Fernandez et al., 2018 has designed liposome contained phosphatidylserine and b-cell autoantigen. Phosphatidylserine accelerated the phagocytosis of liposomes and protected dendritic cells viability. These dendritic cells secreted cytokines, inhibited the proliferation of T cells, and reduced the response of antigen-specific T cells to antigens. They induced the production of regulatory T cells and re-established immune tolerance to dendritic cells to prevent the further development of T1DM [52].

Yu et al. 2017 has prepared insulin-loaded vesicles patches which are self-assembled by hypoxia and H_2O_2 double-sensitive diblock copolymers. When blood glucose level enhance then glucose diffuses through the polymer bilayer membrane and interact with glucose oxidase, which leads hypoxia in the microenvironment, and then the polymersome-based vesicles dissociate and subsequently release insulin. In vivo study result revealed that these insulin patches can effectively regulate and control the blood glucose of type 1 diabetic mice for up to 10 hours [53].

Polymer Nanogel

Nanohydrogels loaded with anti-diabetic drugs are the novel carries for rug delivery according to the change of permeability of the polymer membrane. These Nanohydrogels transform their structure by swelling and shrinking according to pH and temperature changes of media. Nanogels also protect protein drugs from enzymatic degradation, delivery them to reach the intestine unmolested, and effectively control the release rate of preloaded drugs.

Wood K et al. 2018 has prepared pH sensitive hydrogels of methacrylic acid (MAA) and PEG (called P (MAA-g-EG) for oral insulin delivery. The complexation formed by the hydrogen bond between the carboxyl group of MAA and the ether-oxygen of the PEG chain, which made it swelled and dissolved. When reaching the intestinal environment with neutral pH, the sieve pore size of the hydrogel network increased to release drugs to the target site [54-56].

ISSN: 0975-8585

CONCLUSION

Diabetes is a universal epidemic and vulnerable disease which affected larger number of patients. The crucial goal of all therapeutics for the treatment of diabetes mellitus is to attain normal blood glucose levels in the body. Currently available anti-diabetes therapeutic molecules are only managing diabetes symptoms and its progression but not able to cure it properly and they also various side effects. Scientist and researcher are continuously working for the development of newer lead molecules with insertion of novel drug delivery technology for complete cure from diabetes mellitus without any side effects. The brief study of diabetes mellitus etiology helps to researcher for the development of newer anti-diabetic drugs with novel carrier and targeted for better therapeutic action.

AUTHOR CONTRIBUTIONS

Conceptualization, R.K.C.; validation, B.P.; formal analysis, B.P.; investigation, B.P.; resources, R.K.C.; data curation, B.P.; writing—original draft preparation, B.P.; writing—review and editing, R.K.C.; visualization, B.P.; supervision, R.K.C.; funding acquisition, R.K.C. All authors have read and agreed to the published version of the manuscript.

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