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NDDS: Carving a Niche in the Treatment and Management of Diabetes

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Abstract

Diabetes is an incessant metabolic disorder that is defined by an increment in the level of glucose. Type 1 diabetes, which results from insufficient endogenous production of insulin by pancreatic beta cells, as well as abnormalities in the secretion and/or action of insulin, are the causes of this (type 2 diabetes). The worldwide human population seems to be the canter of a diabetic epidemic. Despite significant advancements in the treatment of diabetes, the number of problems associated with the condition is rising. Parallel to this, novel methods have been developed that have been found to reduce the risk of difficulty and are more advantageous. This article emphasizes the development of the modernistic method of synthetic drugs and their therapeutic usefulness in treatment and Management of Diabetes

1. INTRODUCTION

In diabetic conditions, blood glucose level increases more than the normal level. Hyperglycemia, sluggish fat and protein metabolism, and reduced insulin secretion are all symptoms of the metabolic condition of diabetes mellitus.[1]

In California more than 2.3 million adults and in United State 25.8 million children and adults have diabetes. California has increased the percentage of diabetes that is about 35 percent in the last 10 years.[2] Type 1 type of diabetes is found in about 5% of diabetes cases and type 2 is in about 95% of all diabetes cases Type 2 diabetes is more common.[3]

2. CAUSES

A significant risk factor for developing diabetes is obesity.

A growing body of research shows that sugary beverages –because they contain a high proportion of sugar level cause diabetes. These high sugar contents lead to the converted sugar into fat in the liver, which contributes directly to the development of diabetes.

Another cause of developing type-2 diabetes is drinking soda.

Diabetes Mellitus and its related complications are associated with resulting from the imbalance in the production of free radicals that Reactive Oxygen Species (ROS).[1]

3. TYPES OF DIABETES

There are mainly two types of Diabetes:

1. Diabetes Mellitus
2. Diabetes Insipidus

As shown in Fig. 1 Diabetes mellitus can be further classified into four types.[4]

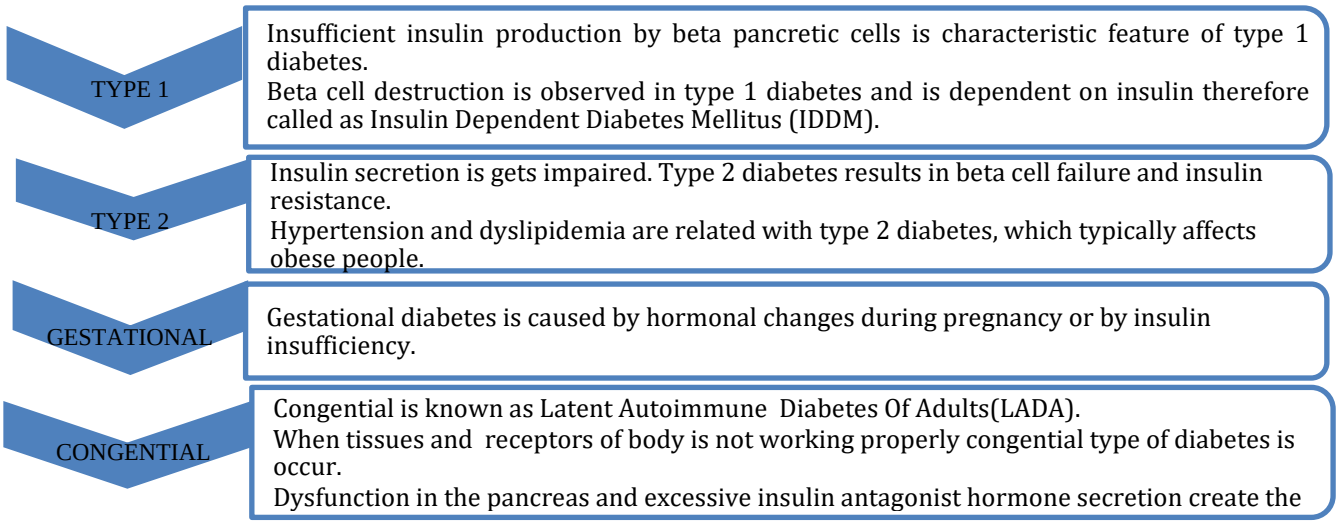

Fig 1: Types of Diabetes mellitus.

4. VARIOUS MEDICINES AND THERAPIES USED IN DIABETES

4.1 CONVENTIONAL MEDICINES

The oral hypoglycemic agents can be classified as shown in Table. 1.

Table 1: Classification of oral hypoglycaemic drugs

Chemical Classes	**Generation and example**	
Sulphonyl Urea	1st Generation	Tolbutamide, Chlorpropamide
	2nd Generation	Glibenclamde (Glyburide) Glipizide, Gliclazide
Biguanides	Metformin	
Meglitinides Phenyl Alanine Analogue	Repaglinide Nateglinide	
Thiazolidiones	Rosiglitazone Pioglitazone	
***α*-Glucosidase Inhibitors**	Acarbose Miglitol	

i. Sulphonyl Urea:-

Mechanism of Action: They act by blocking the conductance of ATP-sensitive K+ channels on the pancreatic B cell membrane, depolarizing the cell, and calcium influx promotes degranulation.[5]

It works by increasing pancreatic insulin release and decreasing post-absorptive rates of endogenous glucose generation.[6]

ii. Biguanides :

Mechanism of Action- It lowers hepatic glucose synthesis while raising peripheral glucose uptake and insulin sensitivity.[6]

They do not stimulate pancreatic β-cells.

1. The main activity is to inhibit the liver's production of glucose and hepatic gluconeogenesis.
2. Muscles and lipids have increased glucose disposal. They improve GLUT 1 transport from the intracellular site to the plasma membrane but do not affect the translocation of GLUT4, the main glucose transporter in skeletal muscle. Thus, the impact is distinct from that of insulin.
3. Slows down the absorption of vitamin B_{12}, amino acids, and other substances through the gut.
4. By enhancing the anaerobic glycolysis mitochondrial respiratory chain promotes peripheral glucose utilization. To the mitochondrial membrane, metformin binds less fervently, though.[5]

iii. Meglitinide or o-Phenylalanine Analogues:

Mechanism of action: -An oral hypoglycemic with a meglitinide analog that is intended to normalize mealtime glucose fluctuations. Although it is not a sulfonylurea, it behaves analogously by attaching to sulfonylurea receptors as well as to other

specific receptors, causing the closure of ATP-dependent K+ channels, which results in depolarization and insulin release.[5]

iv. Thiazolidinediones:

Reduces insulin resistance in peripheral tissue by stimulating PPAR-γ selective agonists for the nuclear peroxisome proliferator-activated receptor (PPAR-γ), which causes the transcription of numerous insulin-responsive genes.[6]By promoting GLUT4 expression and translocation, insulin resistance is overcome, improving glucose entry into muscle and fat. Additionally inhibited is hepatic gluconeogenesis. Activating genes that control fatty acid metabolism and lipogenesis in adipose tissue aids in insulin sensitization.[5]

v. α Glucosidase Inhibitors:

The final enzymes for digesting carbohydrates at the brush border of the small intestinal mucosa, -glucosidases, are inhibited by it. Polysaccharide and sucrose digestion and absorption are slowed and reduced as a result.[5]

4.2 NEWER APPROACHES IN THE MANAGEMENT OF DIABETES

GLP 1

GLP-1 (glucagon-like peptide-1) and GIP (glucagon-dependent insulinotropic peptide) are two major incretins. GLP-1 and GIP stimulate the release of insulin from beta pancreatic cells. GLP-1 inhibits gastric emptying by decreasing pancreatic beta cell glucagon secretion. It has an immediate suppressive effect on the appetite centers.

For the treatment of type 2 diabetes, Exenatideis the first glucagon-like peptide 1 (GLP-1) agonist used.GLP-1 is a gut-derived incretin hormone. Incretin hormones are released in response to nutrient intake, increasing insulin release even before blood glucose levels rise. GLP-1 is an incretin hormone that enhances the production of insulin in response to a meal, inhibits the release of glucagon, delays the emptying of the stomach, curbs hunger, and encourages the growth and regeneration of pancreatic beta cells.[7]

DPP-IV inhibitors

Due to its rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-IV), it is difficult to use in clinical settings. Exenatide is a synthetic GLP-1 analog with similar actions to those of DPP-IV but is resistant to it. It accelerates the release of insulin, suppresses glucagon, and slows down gastric emptying.[5]

Sodium-glucose transporter-2 inhibitors

A novel class of drugs called sodium-glucose transporter-2 (SGLT2) inhibitors is used to treat diabetes.

The other SGLT isoform, SGLT1, has much less involvement in the kidney than it does in the gastrointestinal tract as the primary transporter for glucose absorption. Sodium-glucose transporter-2, which reabsorbs filtered glucose, is present on the proximal convoluted tubule and plays a major role in glucose homeostasis. In diabetic patients, there was increased expression of SGLT2 and other renal glucose transporters. Due to their ability to reduce plasma glucose levels without increasing excessive insulin secretion and their higher selectivity for SGLT2 over SGLT1, SGLT2 inhibitors have a significant advantage over SGLT1 inhibitors as potential anti-diabetic medications.

Canagliflozin, an SGLT2 inhibitor taken orally, improves T2DM glycemic management by reducing the renal threshold for glucose reabsorption and increasing urine glucose excretion, resulting in weight loss.[6]

Insulin

Insulin plays an important role in the control of hyperglycemia in type 1 diabetes patients, whereas it is required later or in certain individuals in type 2 diabetes patients.[8]In the pancreatic islets' beta cells, insulin is produced. In a human pancreas, the exocrine parenchyma of the gland is home to nearly 1 million pancreatic islets.[9]Almost 1,000 endocrine cells, 75% of which are insulin-producing beta cells, are found in each pancreatic islet. In the secretary granules, insulin is converted from its pro-insulin state in the endoplasmic reticulum to its biologically active form. Diabetes patients can significantly lower their blood glucose levels with the help of insulin therapy.

Recombinant technology was used to create human insulin analogs, which is a significant advance.[10]Currently, accessible insulin delivery methods include pens, jet injectors, insulin infusion pumps, and syringes. Subcutaneous injections are the method used to administer insulin. The ultimate objective is to restore patients' ability to generate and use insulin, hence obviating the need for an exogenous insulin supply. Glycemic control in type 1 diabetes typically requires three or more insulin injections per day.[11]

4.3 NOVEL ASPECTS

The performance of an existing drug molecule can be improved in terms of patient compliance, safety, and efficacy by converting it from its conventional form to a novel delivery system. Novel Drug Delivery System an existing drug molecule may gain new life.[12]A significant improvement in drug release at specific locations and rates is the Novel Drug Delivery System. Pharmaceutical companies have been motivated to work on the development of new drug delivery systems by the need to deliver medications to patients effectively and with the fewest side effects.[13]

New concepts for regulating the pharmacokinetics, pharmacodynamics, non-specific toxicity, and efficacy of pharmaceuticals have emerged from interdisciplinary approaches that integrate polymer science, revolutionary pharmaceutical technology, and molecular biology. There are numerous medication delivery and targeting systems being developed right now to decrease drug degradation and loss, avoid negative side effects, boost drug bioavailability, and raise the amount drugs stored in the necessary zone.[14]

To meet the demands of the healthcare industry, new drug delivery systems are being created to get around the drawbacks of existing ones. These systems fall under the categories of targeted drug delivery systems and controlled drug release systems.

The therapeutic benefits of these new systems include[12]

- Increasing the drug's effectiveness
- Targeted delivery system
- Reduced toxicity and adverse effects
- Increased patient convenience
- Successful treatments for diseases that were once incurable
- Potential for prophylactic applications
- Improved patient compliance

According to the literature, the field of drug delivery has advanced tremendously over the past ten years, and several carrier systems have gained prominence.

Classification of NDDS:-

Various Novel Drug Delivery Systems are deduced as follows:

1. Carrier-based Drug Delivery System:
   a) Microparticulates
   b) Liposomes
   c) Nanoparticles
   d) Niosomes
2. Transdermal Drug Delivery Systems

1. Carrier-based Drug Delivery System

a) Microparticulates

Drug release to the targeted treatment site and the formulation of different drug-polymer combinations are two topics covered by microparticle-based therapy. By regulating their release, this aids in preserving the therapeutic concentration of drugs in plasma for a longer period.

Because they are small, microparticles have higher surface-to-volume ratios and can be created to increase the rate at which practically insoluble drugs dissolve.[15]By using microencapsulation techniques, adjusting the drug-polymer ratio, etc., variables like dose and release kinetic are occasionally changed as needed to achieve an optimal therapeutic concentration of the drug in the systemic circulation.[16]Systems with microparticulate content formulated for parenteral, nasal, topical, and oral administration. The concept of microencapsulation has been used to enhance in vivo hypoglycemic effect and modify drug release patterns of drugs.[17]

b) Liposomes

One or more phospholipid bilayers make up the vesicles known as liposomes. The polar aspect of the liposomal core enables the encapsulation of polar medicinal compounds. According to their affinity for the phospholipids, amphiphilic and

lipophilic compounds are solubilized within the phospholipid bilayer. Vesicle membranes can act as a size-selective filter that only enables the passive diffusion of tiny solutes like ions, nutrients, and antibiotics by incorporating channel proteins into the hydrophobic part of the membrane. Drugs that are capsuled successfully protect channel proteins from early proteolytic enzyme breakdown.[16]

c) Nanoparticulate

There are crystalline, amorphous, and solid types of nanoparticles. They can adsorb or encapsulate a medicine to protect it from enzymatic and chemical deterioration.[18]Biodegradable polymeric nanoparticles have drawn a lot of interest because they could be used to deliver drugs to specific organs and tissues, carry DNA for gene therapy, and deliver proteins, peptides, and genes orally.[19]

d) Niosomes:-

Niosomes are being studied as an alternative to liposomes, which have several drawbacks, including the following: due to their susceptibility to oxidative deterioration, phospholipids, one of its constituents, are chemically unstable and require particular treatment and storage. Additionally, the quality of naturally occurring phospholipids varies. Niosomes are made from a single-chain uncharged surfactant and cholesterol. Niosomes functions like liposomes, thus increasing the circulation of entice drugs and developing organ distribution and metabolic stability. Such vesicular drug carrier systems modify the drug's metabolism, tissue distribution, plasma clearance kinetics, and cellular interaction. They should direct the medication to the intended site of action and/or regulate its release. Niosomes can be used for a variety of drug delivery methods, including targeted, ophthalmic, topical, and parenteral.

2. Transdermal Drug Delivery System:

Transdermal drug delivery is the application of self-contained, discrete dosage forms to intact skin to deliver drugs to the bloodstream at a controlled rate. The transdermal drug delivery system (TDDS) became a crucial component of cutting-edge drug delivery systems.[20] Transdermal route is more convenient and safe thus it is the most preferred route for administration and most accepted by patients. The advantages of delivering drugs through the skin to achieve systemic effects are as follows [16]

- First-pass metabolism is avoided
- Avoiding gastrointestinal incompatibility
- Activity duration is predictable and improving physiological and pharmacological response
- Therapy can be stopped at any time with ease
- Higher patient adherence as a result of the removal of multiple dosing profiles
- Suitability for self-management
- Enhance therapeutic efficacy

Table 2 discusses various examples with their advantages with new formulations of known drugs.

Table 2: Novel drug delivery of a few drugs with their advantages

NDDS	Anti-diabetic drug	Advantages
Microparticles	Insulin	1.Preserved bioactivity 2.Improved proteolytic stability 3.Oral/nasal delivery 4.Protection against the stomach's acidic pH 5.Enhancing biodistribution
	Glipizide	Reduced dosage frequency, obtained sustained release, and reduced dose-related side effects
	Glimepiride	Improved dissolution rate
Liposomes	Insulin and peptide surrogate	1.Increased pulmonary retention time and as a result, extrapulmonary side effects were reduced 2.Proteolytic stability has been improved in oral administration, as it has chemically responsive release 3.Sustained release and transmucosaldelivery[21]

Nanoparticles	Insulin	1.Provided a non-invasive method of delivery 2.Encourage patient self-administration 3.Improved effectiveness even for 22 days 4.Compared to the insulin solution, there is a bioavailability improvement of up to 350%, 5.Nasal administration improves systemic absorption 6.Improved hypoglycaemic effect and permeability, 7.Retained bioactivity, 8.Targeted to the colon for better absorption[22]
	Metformin	1.Reduced dosing frequency[23]
	Glibenclamide	1.Improved dissolution rate[24]
	Repaglinide	Provided a delayed release and prevented a [25]
Niosomes	Insulin and peptide drugs	1.Protected from enzymatic deterioration in oral, 2.Prolonged bioactivity for 6 hrs.[26]
Transdermal systems	Glipizide	Avoid adverse effects like anorexia and fatal hypoglycemia, as well as gastrointestinal disturbances like nausea, vomiting, heartburn, and heartburn i.e. in connection with oral delivery [27]
	Insulin	1.Served as a perfect substitute for injectables 2.Controlled release for at least 8hrs

The field of drug delivery is continually inventing and developing to increase the effectiveness of intelligent drug delivery systems in order to maximize therapeutic efficacy and minimize unfavourable side effects. Because every delivery system has different pharmaceutical and physiological properties, careful consideration of independent variables is essential when designing the final product.

5. CURRENT STATUS AND FUTURE PROSPECTS

Despite the recent avalanche of new medications to treat and prevent the condition, diabetes is spreading widely and its popularity is increasing. Perhaps the most pessimistic ascent of all is that the rise is even emulated in children. Nanotechnology is a rudimentto change the spectrum and methods of visual imaging and drug delivery.[28]Nanomedicine initiatives visualize the Nanoscale technologies; will acquiescent more medical benefits within the next 10 years. Instead of pushing applications for some materials, the future of nanomedicine depends on the cognitive design of nanotechnology tools and materials based on a thorough understanding of biological processes. Synthetic medicine preparations should not be considered just as a collection of therapies. They are formulated and prepared to keep in mind the conditions of sickness and the mending properties of individual ingredients.[29] It is important, therefore, that the medicines and preparations should be taken into forethought of their integrated analeptic approach. Table 3, illustrates a few examples of some approved products already in the market.

Table: 3 Some Marketed product[31]

Therapeutic name	Trade name
New-generation insulins	Tresiba Ryzodeg®70/30 Xultophy®*
Glucagon-Like Peptide-1	Victoza®
Modern insulins	Novo Rapid® ** Novo Rapid® Pump Cart® Levemir® Novo Mix® 30 Novo Mix® 50 Novo Mix® 70
Human insulins	Insulatard® Actrapid® Mixtard® 30 Mixtard® 40 Mixtard® 50
Oral antidiabetic agents	Novo Norm®
Diabetes devices	FlexTouch® Flex Pen® Novo Pen® 4 Novo Pen® 5 Novo Pen Echo® Inno Let®

6. CONCLUSION

Synthetic therapy for diabetes has been widely accepted all over the World successfully. Synthetic medicines are always more effective and frequently used to treat Type 1 and Type II diabetes and its complications. The medicines mentioned in this paper have been considered for their possible hypoglycaemic actions. Utilizing a multifaceted approach, new chemical entities will focus on treating metabolic disorders.[30]Future antidiabetic treatment approaches may not only manage diabetes symptoms and alter the disease's course, but also possibly prevent or cure it. T2DM can currently be managed with a variety of medications, however practically all of them come with limitations and don't treat all of the problems that diabetic individuals have. In patients who have failed conventional oral therapies, insulin therapy is always an option. However, some concern has been raised by preliminary studies indicating an increase in mortality in HF patients treated with this, the most effective glucose-lowering agent.[7]

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8. CONFLICT OF INTEREST

Authors have no conflict of interest with anyone.

9. BIBLIOGRAPHY

1. J. Ozougwu, K. Obimba, C. Belonwu, and C. Unakalamba, "The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus," *J. Physiol. Pathophysiol.*, vol. 4, no. 4, pp. 46–57, 2013.
2. S. Bastaki, "Review Diabetes mellitus and its treatment," *Int J Diabetes Metab.*, vol. 13, pp. 111–134, 2005.
3. C. D. Deshmukh and A. Jain, "Diabetes Mellitus : A Review," *Int. J. Pure Appl. Biosci.*, vol. 3, no. 3, pp. 224–230, 2015.
4. S. A. Mohammed *et al.*, "Journal of Medicinal Plants Research Review on diabetes, synthetic drugs and glycemic effects of medicinal plants," vol. 7, no. 36, pp. 2628–2637, 2013.
5. K. Tripathi, *Essentials of Medical Pharmacology, K.D. Tripathi*, 6th ed. 2008.
6. M. Safavi, A. Foroumadi, and M. Abdollahi, "The importance of synthetic drugs for type 2 diabetes drug discovery," *Expert Opin. Drug Discov.*, vol. 8, no. 11, pp. 1339–1363, 2013.
7. S. E. Inzucchi and D. K. McGuire, "New drugs for the treatment of diabetes part II: Incretin-based therapy and beyond," *Circulation*. 2008.
8. S. Yaturu, "Insulin therapies: Current and future trends at dawn," *World J Diabetes*, vol. 4, no. 1, pp. 1–7, 2013.
9. M. Volume, "Effects of insulin in relatives of patients with type 1 diabetes mellitus," *N Engl J Med*, vol. 346, no. 22, 2002.
10. J. Green, G. Buchan, and A. Swanson, "Hereditary and Idopathic Types of Diabetes Insipidus," *Brain*, 1967.
11. S. Georg**,** A.Roy"Novel approaches in Insulin Drug Delivery," *Int. J. Drug Dev. Res.*, vol. Vol. 5, no. 4n, pp. 25–29, 2013
12. R. R. Bhagwat, and I.S. Vaidhya "Novel Drug Delivery Systems: An Overview" *Int. J. of Pharm. Sci and Res.* vol. 4, no. 3, pp. 970–982, 2013.
13. R. P. Swain *et al*, Bridging Between Disease, Prevalence, and Treatment of Diabetes Mellitus : A Review, *Int. J. of Pharm.Tech. Res.,* Vol.7, No.2, pp 212-228, 2015.
14. M. N. Piero, "Diabetes mellitus – a devastating metabolic disorder," *Asian J. Biomed. Pharm. Sci.*, vol. 4, no. 40, pp. 1–7, 2015.
15. B. Pavan Kumar, I. S. Chandiran, B. Bhavya, and M. Sindhuri, "Microparticulate Drug Delivery System: a Review," *Indian J. Pharm. Sci. Res.*, vol. 1, no. 1, pp. 2248–9126, 2011.
16. V. Kumar Rai, N. Mishra, A. Kumar Agrawal, S. Jain, and N. P. Yadav, "Novel drug delivery system: an immense hope for diabetics."
17. S. Chahed *et al.*, "Increased vitreous shedding of microparticles in proliferative diabetic retinopathy stimulates endothelial proliferation," *Diabetes*, vol. 59, no. 3, pp. 694–701, 2010.
18. G. Sharma, A. R. Sharma, J.-S. Nam, G. P. C. Doss, S.-S. Lee, and C. Chakraborty, "Nanoparticle based insulin delivery system: the next

generation efficient therapy for Type 1 diabetes.," *J. Nanobiotechnology*, vol. 13, no. 1, p. 74, 2015.

19. E. Gundogdu and A. Yurdasiper, "Drug transport mechanism of oral antidiabetic nanomedicines," *Int. J. Endocrinol. Metab.*, vol. 12, no. 1, pp. 1–5, 2014.
20. S. C. Joshi and N. D. Jasuja, "Enhancement Of Transdermal Delivery System And Antidiabetic Approach: An Overview," *Int J Pharm*, vol. 2, no. 1, pp. 129–141, 2012.
21. A. K. Agrawal, H. Harde, K. Thanki, and S. Jain, "Improved stability and antidiabetic potential of insulin containing folic acid functionalized polymer stabilized multilayered liposomes following oral administration," *Biomacromolecules*, vol. 15, no. 1, pp. 350–360, 2014.
22. X. Zhang, H. Zhang, Z. Wu, Z. Wang, H. Niu, and C. Li, "Nasal absorption enhancement of insulin using PEG-grafted chitosan nanoparticles," *Eur. J. Pharm. Biopharm.*, vol. 68, no. 3, pp. 526–534, 2008.
23. M. Cetin, A. Atila, S. Sahin, and I. Vural, "Preparation and characterization of metformin hydrochloride loaded-Eudragit®RSPO and Eudragit®RSPO/PLGA nanoparticles.," *Pharm. Dev. Technol.*, vol. 18, no. 3, pp. 570–6, 2013.
24. L. Yu, C. Li, Y. Le, J. F. Chen, and H. Zou, "Stabilized amorphous glibenclamide nanoparticles by high-gravity technique," *Mater. Chem. Phys.*, vol. 130, no. 1–2, pp. 361–366, 2011.
25. U. M. Dhana lekshmi, G. Poovi, N. Kishore, and P. N. Reddy, "In vitro characterization and in vivo toxicity study of repaglinide loaded poly (methyl methacrylate) nanoparticles," *Int. J. Pharm.*, vol. 396, no. 1–2, pp. 194–203, 2010.
26. A. Pardakhty, J. Varshosaz, and A. Rouholamini, "In vitro study of polyoxyethylene alkyl ether niosomes for delivery of insulin," *Int. J. Pharm.*, vol. 328, no. 2, pp. 130–141, 2007.
27. S. Mutalik, N. Udupa, S. Kumar, S. Agarwal, G. Subramanian, and A. K. Ranjith, "Glipizide matrix transdermal systems for diabetes mellitus: Preparation, in vitro and preclinical studies," *Life Sci.*, vol. 79, no. 16, pp. 1568–1577, 2006.
28. Ashok K. Tiwari and Madhusudana Rao, "Diabetes mellitus and multiple therapeutic approaches of phytochemicals: present status and future prospects," *Curr. Sci.*, vol. 83, no. 1, pp. 30–38, 2002.
29. Moein Moghimi, "Nanomedicine: current status and future prospects," *FASEB J.*, vol. 19, no. 3, pp. 311–330, 2016.
30. R. Aathira and V. Jain, "Advances in management of type 1 diabetes mellitus.," *World J. Diabetes*, vol. 5, no. 5, pp. 689–96, 2014.
31. B. L. B. Cohen, D. Pharm, C. M. George, and B. a Hemstreet, "New Technologies for Managing Diabetes Mellitus," 2010.