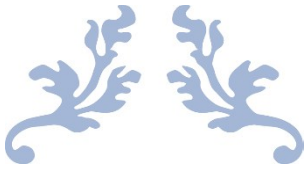

Chapter 1

Introduction

1. Background: Diabetes mellitus

Diabetes mellitus (DM) is a category of metabolic disorders characterized by hyperglycemia due to deficiencies in insulin secretion, insulin action or both.[1] As a result of ageing, urbanization and associated lifestyle changes, the global prevalence of DM is increasing rapidly.[2] DM is recognized as the eighth leading cause of death worldwide and is spreading very rapidly, particularly in low- and middle-income countries, with an overall prevalence rate of 8.5 percent in adults.[3] According to the International Diabetes Federation, the number of people diagnosed with diabetes worldwide increased explosively from 151 million in 2000 to 463 million in 2019 and this number is projected to reach 578 million by 2030, and 700 million by 2045.[4] In 2019, more than one million children and adolescents were reported to have type 1 diabetes mellitus (T1DM). Total healthcare spending on diabetes in 2019 was USD 760 billion and is expected to increase to USD 845 by 2040.[5-7] Such soaring figures need aggressive research not only to develop new molecules for efficient diabetes treatment, but also to develop alternative therapeutic approaches through the use of nanotechnology to overcome the problems associated with traditional approaches to the drug delivery.

In the development of DM multiple pathogenic processes are involved. This range from autoimmune disruption of the pancreatic β-cells with consequent deficit of insulin to abnormalities that result of insulin resistance. Deficient insulin action on target tissues is the cause of these metabolic anomalies.[8] Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses towards insulin at one or more steps in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone

or both, is the primary cause of the hyperglycemia.[9] There are four clinical classes of diabetes including type 1, type 2, other specific types of diabetes (genetic defects in ß-cell function or insulin action, disease of exocrine pancreas, drug- or chemically induced diabetes) and gestational diabetes mellitus (GDM).[10,11] Majority of diabetes cases fell into two broad groups of etiopathogens. In one type, T1DM, the cause is an absolute insulin secretion deficiency. Individuals at increased risk of developing this type of diabetes can often be identified by serological evidence of an autoimmune pathological process occurring in the pancreatic islets and by genetic markers.[12] In the other, far more predominant category, type 2 diabetes mellitus (T2DM), the cause is a combination of insulin resistance and an insufficient compensatory insulin secretory response.[1,13] For the purpose of this thesis, discussion will be mainly focused on T1DM.

2. T1DM: causes, current status and treatment

T1DM is triggered by an autoimmune reaction in which the body's immune system damages the insulin-producing β cells of the pancreas.[14] This results in either little or no insulin being released by the body. The origins of this inflammatory mechanism are not well known but a probable scenario is that the combination of genetic vulnerability (conferred by a wide number of genes) and an environmental stimulus, such as a viral infection, initiates the autoimmune reaction.[15] Once stimulated, macrophages secrete multiple inflammatory cytokines including interleukin-1β (IL-1β), interleukin-12 (IL-12) and tumor necrosis factor α (TNF-α) arising from stimulated T cells. [12,16] Such cytokines destroy the β-cells by causing oxygen-free radicals, nitric oxide and lipid peroxides within the β-cells and enhance Th1 cell-mediated inflammatory

responses.[17] Toxins, or certain dietary factors, were also associated with development of T1DM. The condition can occur at any age although T1DM is more severe in children and adolescents.

Strong glycemic regulation in T1DM decreases the risk of development and progression of late diabetic microvascular complications and also has long-term beneficial effects on the development and progression of nephropathy, hypertension, cardiovascular diseases and atherosclerosis.[18] Existing therapies have limited effectiveness, limited tolerability and substantial mechanism-based side effects such as weight gain and episodes of hypoglycemia. Moreover, only a handful of the treatments available which can sufficiently tackle underlying risks, such as obesity and/or insulin resistance. Thus, newer approaches are the need of the hour with greater emphasis on exploring delivery approaches that rely on physiological responses (e.g., glucose-mediated insulin secretagogues) without substantial weight gain.[19,20]

Despite the development of active anti-hyperglycemic agents, the major challenges in successful diabetes treatment include improving the existing therapies to maintain an acceptable and controlled glucose level and resolving the long-term complications associated with diabetes.

2.1. T1DM and insulin: treatment and limitations

The gold standard in T1DM therapy is functional insulin therapy with a system in basal-bolus insulin. Different insulin regimens used for treating T1DM patients include short-acting, long-acting, and premixed human insulin and insulin analog preparations. Short-acting analogs of insulin include Insulin lispro (Humalog ®), Aspart (Novorapid ®) and Glulisine (Apidra ®) that work for up to 3-5 hours. Long-acting analogs of insulin include Insulin Glargine (Lantus ®) and Detemir (Levemir ®) with an effect lasting less than 24 hours.[21] However, intense insulin therapy also raises the risk of hypoglycemia. Despite the emergence of modern insulin analogs

with physiologically appropriate absorption profiles and less routine bioavailability differences relative to older insulin preparations; varying blood glucose levels, which often raise the risk of hypoglycemia, remain a serious threat. There are shortcomings in T1DM treatment with prolonged insulin therapy and many patients do not obtain the required blood glucose levels and metabolic targets.[22,23] Firstly, insulin tackles only partly the paradoxical and pathophysiological glucagon abundance. Secondly, in individuals with T1DM, the gastric emptying rate is changed and even the fastest acting mealtime insulin peaks are too late to balance postprandial glucose absorption, leading to significant postprandial glucose excursions.[24,25] Thirdly, intense insulin therapy is often associated with weight gain, potentially increasing cardiovascular risks, leading to hyperglycemia.[26] Obesity is a massive problem in T1DM, with an approximate prevalence of about 50 percent in some developing countries.[27] Thus, novel non-insulin adjunct therapies need to be explored in patients with T1DM.

2.2. Conventional oral anti-diabetic formulations: treatment and limitations

The best treatment for T1DM is currently combination therapy using medications with actions complementary to insulin that can boost glycated hemoglobin (HbA1c), reduce the risk of hypoglycemia, cardiovascular disorders and weight loss. Glucagon-like peptide-1 (GLP-1) receptor agonists and pramlintide inhibit glucagon secretion, and slow gastric emptying.[28,29] Dipeptidyl peptidase-4 (DPP-4) inhibitors raise endogenous GLP-1 concentration by 2-3 times, potentiating glucose-dependent insulin release and glucagon inhibition.[30] Insulin resistance is evident in even lean T1DM patients. Thiazolidinedione primarily enhances insulin sensitivity and this effect is also associated with weight gain, while sulfonylureas only potentiate insulin secretion and therefore no significant impact on glucose levels or insulin dose will be expected in

patients without β-cell function with these medications. Metformin also decreases the production of hepatic glucose and causes a minor weight loss, but its treatment for T1DM patients is not recommended in any international guidelines as it raises the risk of adverse gastrointestinal events.[31] Sodium-glucose co-transporter-2 (SGLT2) inhibitors reduce reabsorption of renal glucose, resulting in substantial glucose excretion in urine. Since the mode of action of SGLT2 inhibitors is insulin independent, if used in patients with T1DM a significant impact of these drugs on glucose regulation can be anticipated.[32]

These oral anti-diabetic medications have some drawbacks and are usually used in combination with insulin in the treatment of T1DM patients. Solubility and permeability challenges are quite popular among these anti-diabetic drugs which are already present in the market. Some oral anti-diabetics like sulfonylureas, have poor solubility which contributes to less bioavailability and hence a frequent dosage regime that results in non-compliance by the patient due to the missed dose.[33] At the other hand, metformin, frequently used as a first-line medication for T2DM, belongs to the Biopharmaceutical Classification System (BCS) class III and is thus highly soluble but poorly permeable leading to its slow and insufficient absorption.[34,35] Shortcomings seen with several other anti-diabetic medications are short half-life (3-5 h) with thiazolidinedione like pioglitazone resulting in poor bioavailability and decreased therapeutic efficacy.[36,37] Repaglinide, often used as an alternative drug as an adjunct therapy, also has a limited half-life (~1 h) and has to be given three times a day, frequently contributing to patient non-compliance.[38] The marketed formulations of GLP-1 agonists that is Byetta® for exenatide and Victoza® for liraglutide, have a limited half-life and are given solely by s.c. route which often causes discomfort to the patient like injection site (ISR) reactions such as swelling,

pruritus, local pain and chances of infection. In fact, these medications induce nausea and vomiting too.[39-41] In addition to the aforementioned issues, some of the well-known and commonly used anti-diabetic drugs often cause serious hypoglycemia and weight gain. Moreover, such a therapeutic approach does not allow for completely controlled homeostasis of glucose and may result in disorders of the cardiovascular system over time. Hence it is of utmost importance for diabetic patients to find alternative and better therapies using novel drug delivery systems (NDDS).

3. Nanomedicines for diabetes: significance and status

NPs are colloidal drug delivery systems that involve nanocrystals, polymeric nanoparticles, polymeric micelles, solid lipid NPs, nanosuspensions, and multilayer nanoparticles in the size range of 10-1000 nm in diameter. They can be in the form of a matrix system in which the drug is dispersed all across the particles, or as a reservoir system in which the drug is enclosed to a cavity covered by a polymeric membrane. [42-44]

Nano formulations not only enhance the drug's solubility but can have many other advantages such as decreased dosage, rapid onset of action, controlled release of drugs, minimized side effects, targeted drug distribution, enhanced half-life of the drug, decreased patient to patient variability as well as improved bioavailability, and thereby can solve several of the drawbacks of existing anti-diabetics.[45-48] To mention a few examples; many studies indicated an increased area under curve (AUC) and higher bioavailability of sulfonylureas when delivered by nanoformulations due to its enhanced solubility.[49-51] Several sustained release nanoformulations were also reported to address the permeability problems of metformin.[52-54] Hasan et al. observed a two-fold improvement in AUC of metformin niosomes relative to pure

drug solution.[55] Nanotherapy has found a way to overcome the short half-life obstacle; pioglitazone nanostructured lipid carriers embedded in a transdermal patch (TDP) substantially reduced BGL to 24 hr relative to the commercial formulation (6 hrs).[56] Nanoformulations have also been effective in addressing limitations linked to high dose frequency by allowing the medication to be released sustainably. A sustained release of the repaglinide from its nanoformulations revealed a robust hypoglycemic effect relative to the already marketed preparations.[38,57] Furthermore, when delivered orally, nanoformulations of GLP-1 analogs demonstrated an improved hypoglycemic effect with comparable AUC compared to s.c. administration of drug solution.[48,58]

Most interestingly, nano formulations often act at the molecular level to facilitate cellular drug uptake or block efflux pathways such as P-glycoprotein (P-gp) pump or via targeting specific receptors, thus further improving the pharmacokinetic and pharmacodynamic profile of anti-diabetic drugs. TPGS-based repaglinide nanocrystals inhibited the P-gp efflux pump by rigidizing the membrane lipid bilayers as well as inhibited the CYP3A4 enzyme which is responsible for metabolizing the drug in the liver, contributing to a substantial improvement in repaglinide bioavailability.[59,60] Glibenclamide's bioavailability has also been enhanced by formulating SLNs containing Compritol 888 ® ATO which form chylomicrons and thus enhance the drug's lymphatic transport. Improved surface area and decreased efflux transport by these SLNs are also responsible for the drug's improved bioavailability.[61] In another study on preventing drug efflux from the cells, glibenclamide SNEDDS showed better uptake and therefore higher bioavailability of the drug by inhibiting efflux transporters of ATP-binding cassette (ABC) that are known to transport glibenclamide out of the cells. This was because of

the presence of Tween 80, Cremophor RH, TPGS and Brij 30 in glibenclamide SNEDDS.[50] Up on oral administration of Fc receptor targeting exenatide NPs showed increased hypoglycemic activity compared to pure drug injection by s.c route and greater gastrointestinal retention compared to unmodified NPs. Fc receptors exist in the small intestine as well as colon and have an expanded surface region for NP absorption.[62] In addition, exenatide loaded albumin and dextran NPs demonstrated higher oral relative bioavailability (77%) due to higher lymphatic absorption of dextran effectively binding to the dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN) receptor family.[48] **Table 1.1** discusses different types of nanoformulations for treatment of DM.

4. Lisofylline (LSF) as a potential molecule for treatment of autoimmune disorders

LSF was originally developed and tested to reduce cellular damage due to autoimmunity, hypoxia and ischemic reperfusion.[63] LSF has been used to overcome morbidity and mortality during serious infections associated with cancer chemotherapy and for treatment of acute lung injury after severe trauma.[64,65] It has also been reported for its therapeutic efficacy in early treatment of diabetes wherein, it enhances glucose-stimulated insulin secretion,[66,67] causes reversal of insulin insensitivity and glucose-induced phosphorylation of the insulin receptor.[68] The protective role of LSF in diabetes is mainly attributed to the promotion of mitochondrial metabolism in β-cells, normalizing the membrane potential of mitochondria and thus stimulating energy production.[69,70] Mitochondrion controls cell apoptosis[71] and regulates β cell insulin secretion.[14] This broad spectrum of activity suggests that LSF bears significant clinical utility in preventing both T1DM and T2DM.[70,72] Considering the immense therapeutic potential and

multiple pharmacological activities of LSF as stated above, appropriate and improved therapy of LSF is of paramount significance.

5. LSF: Currently under development for treatment of diabetes

LSF has well reported benefit in T1DM. Striffler and Nadler have demonstrated that LSF decreased IL-1β induced islet dysfunction in isolated pancreatic islets along with maintaining insulin secretion. Furthermore, co-incubation of LSF with insulin secreting, rat insulinoma cells, INS-1 in the presence of pro-inflammatory cytokines, IL-1β, TNF-α and IFN-γ, restored glucose-stimulated insulin secretion and mitochondrial metabolism to control levels.[72] LSF treatment in the non-obese diabetic (NOD) mouse model of TIDM delayed the onset of diabetes.[73] In T2DM prediabetic mice, LSF administered at 25 mg/kg, intraperitoneally (IP), twice daily potentiated glucose-mediated insulin secretion possibly by stimulating the functioning of residual β cells.[74]

LSF administration in obese Zucker rats that are well known models for obesity and insulin resistance, reduced p-STAT4 in visceral adipose tissues and showed improvement in metabolic profile of zucker rats by reducing fasting plasma glucose and improving insulin sensitivity. LSF treatment increased feed efficiency with concomitant increased lipid storage in adipose tissue, which may be beneficial in preventing deposition of ectopic (nonadipose) lipids. [75] Yang et al. investigated LSF and exendin-4 (Ex-4) combination (LSF (27 mg/kg/day) and Ex-4 (18 nM/day) were delivered by the Alzet osmotic minipumps to provide a 28 day consistently systemic administration by s.c. route) simultaneously block the autoimmune cytokine damage along with simultaneously supplying a growth-promoting stimulus for β-cells in the non-obese diabetic (NOD) mouse model. The results demonstrated that LSF and exendin-4 combined therapy could effectively and efficiently reverse insulin-dependent autoimmune diabetes in the

NOD mouse model. Although, actual mechanism behind synergistic effect of LSF and Ex-4 was not known. Here, Ex-4 works as an activator of the GLP-1 receptor by activating cyclic AMP and protein kinase A while LSF improves mitochondrial function and blocks the expression of STAT-4 activation in target tissues.[76]

Several researchers have demonstrated the efficacy of LSF in diseases that are either mediated by altered lipid profile or induced by pro-inflammatory cytokines including diabetes. Nonetheless, the low potency, poor oral bioavailability, and short half-life of LSF hinder its clinical translation. Research efforts aiming at improving these shortcomings of LSF are still in infancy.[77]

Inspite of being a potent molecule, LSF is quite less explored in research and very few reports are available focusing on the physicochemical and pharmacokinetic issues associated with LSF. In one such study reported in the year 2006, Cui et al. have synthesized 32 analogs based on the structural motif of LSF wherein, only two of these analogs were found to be effective in protecting β-cells from cytokine-induced injury and maintaining insulin secretory ability in cell culture based evaluation.[69] Nonetheless, no *in vivo* pharmacokinetic and pharmacodynamics data is reported on these analogs till date to determine if the synthesized analogs improved the metabolic stability and oral bioavailability of LSF. We did not come across any other study highlighting the approaches to modify LSF or deliver it by either conventional or novel drug delivery systems.

6. Drug delivery challenges associated with LSF

The broad spectrum of activity of LSF suggests its significant clinical potential but inspite of being a potent molecule it poses certain major challenges that limit its clinical development.

6.1. High aqueous solubility

LSF has a high aqueous solubility (~60 mg/mL in water) which hinders its encapsulation into any delivery system.[72] Due to its hydrophilicity, it exhibits low intracellular absorption, short half-life (~ 0.75-1.17 h), rapid clearance, sub-optimal distribution and poor pharmacokinetics.

6.2. Extensive first pass metabolism and short half-life

LSF undergoes rapid interconversion into PTX necessitating a high dose and frequent dosing for its therapeutic action.[78] LSF has a low (to non-existent) oral bioavailability in humans (~5.9 %) due to its extensive first pass metabolism.[68] Due to these pharmacokinetic issues, it is required in high doses inspite of being potent.

Nadler *et al.* have reported the anti-diabetic potential of LSF in streptozotocin (STZ) induced diabetic model at a dose of 25 mg/kg, i.p., twice daily.[72] Similarly, Yang Z. *et al.* reported the effectiveness of LSF in diabetes prevention in multiple low dose STZ induced diabetic mice model at a dose of 25 mg/kg, i.p. twice daily, for 14 consecutive days.[74] Combination delivery of LSF and β-cell growth factor, exendin-4 has been explored for reversal of autoimmune diabetes in NOD mice wherein, LSF was administered at 27 mg/kg/day by s.c. route using osmotic mini pump for 28 days.[76] In clinical trials of LSF in T1DM, LSF has been administered at a single dose of 9 mg/kg by continuous IV infusion or at 12 mg/kg by continuous subcutaneous infusion over a 10 hour period during the alternate period 1 week apart.[79] Apart from T1DM, in other ongoing clinical trials of LSF for treatment of allogeneic bone marrow transplants[80], acute lung injury and acute respiratory distress syndrome, the drug is administered

Table 1.1

Nanoformulations in diabetes: significance and status

Drug	Drug Delivery System	Dose and ROA	Remarks	Ref
			Nanoparticles (NPs)	
Insulin	Bioadhesive NPs	-----	The formulations of exenatide- or insulin-loaded NPs demonstrated substantial reduction of glycemia in patients with diabetes beginning from 2 h post oral administration.	81
	Chitosan PGA NPs (250 nm and 25 mV)	30 IU/Kg, oral	NPs were prepared by incorporating a solution composed of insulin and -y-PGA to trimethyl chitosan or chitosan using a tripolyphosphate, magnesium sulphate, etc. via process of mild ionic gelation.	82
	PLGA NPs (247 nm and -16.7 mV)	30 & 50 mg/kg orally	Protect insulin from gastric pH. ~25% insulin release was observed after 24 h of incubation at pH 1 but comparatively higher release in PBS 7.4 (~35% in 24 h). NPs showed substantial reduction in glycemia that was sustained for 24 h.	83
	PLGA and HPMCP55 NPs (180 nm)	50 IU/kg, Oral	The formulation of NPs demonstrated a decrease of up to > 80% in glycemia, and also a determined relative bioavailability of 11.3% in diabetic rats.	84
	PLGA NPs consisting of chitosan and stabilized by pluronic 188 (133 nm and 40 mV)	Oral	NPs demonstrated moderately biological adhesion to the rat intestine and comparatively higher reduction in serum glucose levels compared to non-chitosan PLGA NPs. The relative bioavailability was found to be 10.5% and 7.6%, respectively.	85
	Polycaprolactone and Eudragit RS blend NPs (700 nm and +40 mV)	50 IU/kg, oral	NPs demonstrated a reduction in glycemia of up to 53 per cent at 50 IU / kg, which decreased with increased dosage	86
	Chitosan & γ-poly(glutamic acid) NPs (245 nm and 27 mV)	-----	NPs exposed the close junctions of the Caco-2 cell monolayer in vitro transiently and released insulin. Radiolabeled insulin has been shown to be ingested and detected as early as 30 min after administration in the kidney and urinary bladder.	87
Metformin	Chitosan and gum arabic NPs (146.5 ± 8.7 nm)	40 mg/kg orally	Significant reduction in fasting blood glucose as compared to pure metformin (150 mg/kg) administered orally, for 21 days	52

	Alginate NPs (60 – 150 nm)	1.5 g/kg	Significant reduction in blood glucose level as compared to pure metformin (150 mg/kg, i.p.)				54
	Chitosan based non-composite films containing mesoporous MCM-41 (5.8 nm) and MCM-41 (5.93 nm)-aminopropylsilane NPs	----	Prolonged release till 15 days, no cellular toxicity				53
Pioglitazone	Polaxomer 188 and Eudragit L 100 NPs (138.8 nm)	----	Enhanced drug solubility by 10 folds than pure drug and 97.5% drug released within 60 min				88
Glibenclamide	HPMC K15M and lactose NPs (168.6 nm)	5 mg/kg, orally	*PK parameters*	$AUC_{(0-\infty)}$ (ng h/mL)	$t_{1/2}$ (h)	C_{max} (ng/mL)	89
			Pure drug	71680.24±63.6	5.73±0.42	9428.42±897.8	
			NPs	172383.64±237.2	9.57±0.23	24451.14±2170.5	
Repaglinide	Soluplus® (SLPS) and Kolliphor™ E-TPGS nanocrystals, (304±6 nm for 1% w/v SLPS (TD-A) and 331±34 nm for SLPS and 0.5% w/v of TPGS (each) (TD-B))	2 mg/kg, orally	*PK parameters*	$AUC_{(0-\infty)}$, fasted state µg h/L	$AUC_{(0-\infty)}$, fed state µg h/L		59
			Pure drug	25.76±4.17	18.57±6.13		
			TD-A	257.75±7.32	241.63±13.51		
			TD-B	384.07±9.54	355.88±10.69		
Exenatide	Mesoporous silica NPs (SBA-15) (920±120 nm)	50 µg/kg, s.c.	*PK parameters*	AUC (ng h/mL)	MRT (h)	C_{max} (ng/mL)	T_{max} (h)	90
			Free drug solution	1.71±0.07	1.14±0.07	1.16±0.09	0.46±0.02	
			NPs	8.77±0.76	21.3±0.99	0.39±0.01	1.38±0.22	
	Fc modified polyethylene glycol-poly (lactic-co-glycolic NPs (130±5.2 nm)	100 µg/kg, orally	Hypoglycemic effect for 12 h when compared to 8 h by s.c. administration of free drug solution (10 µg/kg). Higher gastric residence time (24 h), when compared with unmodified NPs (10h)				62
Self emulsifying drug delivery systems							

Pioglitazone	Capryol 90, Transcutol HP, Cremophor ELP SMEDDS (< 50 nm)	----	60% drug release in 24 h, when compared with marketed preparation (17%), and pure drug					91
Glipizide	Phosphatidylcholine (Phosal 53 MCT), Tween 80, and Transcutol P SEDDS (55.94 nm) and S-SEDDS (78.03 nm)	800 µg/kg, i.g.	After OGTT, improved reduction in BGL within 30 min, when compared with pure drug suspension (800 µg/kg), i.g., higher bioavailability					92
Glimepiride	Miglyol® 821, Tween 80, PEG 400, aerosol 200 S-SNEDDS (152 nm)	1 mg/kg, orally	Increased $AUC_{(0-24h)}$ for L and S-SNEDDS 248.88±52.22 and 234.64±32.22 respectively as compared to pure drug 128.77±54.25, and marketed formulation 207.20±34.16, orally (1 mg/kg)					51
Glibenclamide	Aerosil 200 (carrier for L-SNEDDS) SNEP (143.6 ± 3.46 nm)	3 mg/kg, orally	In rabbits: significantly higher AUC_{0-24} of SNEPs 220.43±44.22 mg h/mL, when compared with L-SNEDDs (3 mg/kg), 139.34±34.14 mg h/mL and pure drug (3 mg/kg) 103.52± 22.60 mg h/mL, orally					93
Micro- and Nano-emulsion								
Glimepiride	Capryol 90, Cremophor RH 40), Transcutol micro-emulsion (38.9 ± 17.46 nm).	5 mg/kg, i.g.	*PK parameters*	$AUC_{0-48h)}$ (µg min/mL)	$t_{1/2\beta}$ (min)	C_{max} (µg/mL)	T_{max} (min)	94
			Drug suspension	857.43	1690.5	0.87	37.6	
			Glimepiride complex	3384.2	1107.8	5.93	36.3	
			Microemulsion	6242.76	4687.8	14.84	74.6	
Repaglinide	Sefsol-218, Tween 80 and Transcutol nanoemulsion (76.23 nm)	1 mg/kg, orally	1 mg/kg dose was able to reduce the blood glucose level by a maximum of 67%					57
Solid lipid nanoparticles (SLNs) and Nanostructure lipid carriers (NLCs)								
Insulin	Stearic acid and soya phospholipid NPs coated with octaarginine (162 nm and 30 mV)		NPs improved the permeability of insulin in Caco-2 cells by 18.4 folds. Decreased fasting blood glucose by 70% compared to initial fasting blood glucose at 1.5 h and determined relative bioavailability was13.9%					95

	NPs with pluronic F127 & glycerylpalmitosterate (305 nm and -17 mV)		NPs in fasted diabetic rats demonstrated a decrease of ~35 percent in glycemia at 5 to 8 h post administration resulting in a calculated 6 percent bioavailability.						96
Glibenclamide	SLNs of Tween 80, Pluronic F68, Phospholipon 90 G (201.5±1.33 nm)	5 mg/kg, orally	*PK parameters*	$AUC_{(0-\infty)}$ (mg h/mL)	$t_{1/2}$ (h)	MRT (h)	C_{max} (µg/mL)	T_{max} (h)	61
			Pure drug suspension	94.63± 6.65	9.07 ±0.79	11.28±0.48	7.57±0.64	4	
			SLN	333.23 ±88.9	12.69 ±2.94	13.36±1.64	18.87±1.11	2	
	SLNs of Precirol® and lecithin (100.2±4.2 nm)	5 mg/kg, orally	Rapid onset of action in just 1h and sustained effect till 8 h						97
Repaglinide	Lipohydrogel NPs (LHNs) prepared by coating chitosan on solid lipid nanoparticles (SLNs) (287±14 nm)	0.18 mg/kg, IV	Burst release of drug was less in LHN as compared with SLN and free drug solution. Reduced toxicity when compared with SLN						98
Exenatide	NLC of Precirol ATO 5, Miglyol, Tween 80 and Polaxomer 188 (161±4 nm)	200 IU/kg	Synthesized NLC were able to stimulate enteroendocrinal L cells to release endogenous GLP-1. Ex vivo studies on human jejunal tissue did not report any toxicity; no Lactate dehydrogenase release with no effect on concentration of ATP						99
			Vesicular systems						
Insulin	Hepatic-directed vesicle (HDV-1 liposome)	0.05 to 0.4 U/kg	In patients with T2DM under stable metformin therapy, the insulin-loaded liposome HDV-1 was well tolerated and resulted in a significant reduction in postprandial glucose excursions						100
Glimepiride	Span 60, cholesterol niosomes (371.8±23.20 nm)	2 mg/kg, orally	Formulations			$AUC_{(0-48h)}$ (ug h/mL)	C_{max} (ug/mL)	T_{max} (h)	101
			Free glimepiride in saline, 2 mg/kg, orally			1.436±1.65	0.394±0.142	2	
			Marketed tablet (Amaryl) in saline (1 mg/mL), orally			10.42±2.32	1.412±0.0212	2	

			Niosomes	9.633±1.19	0.316±0.032	6	
Co-delivery of metformin and glipizide	Egg phosphatidylcholine, 1,2-dimyristoylphosphatidyl cho- line, 1,2-diplmitoylphosphatidylc holine, 1,2-dis teroylphosphatidylcholin e liposomes (64 ± 6 nm)	----	Increased release of glipizide from 3% to 12% and of metformin from 35% to 64%, in 1 h				102
Nanoformulations in Transdermal patches							
Insulin	Chitosan NPs by polyelectrolyte complex formation (110 nm and 21.63 mV)	Transdermal, 2 IU		$AUC_{(0-60)}$ (µIU h/mL)	C_{max} (µIU/mL)	T_{max} (h)	103
			S.C injection	2614.08	46.68	2	
			Transdermal nano-insulin	3153.36	45.80	8	
Pioglitazone	NLC of Carbopol, Tween 80, labrasol, triethanolamine and apifil (166.05 nm)	Transdermal patch		$AUC_{(0-\infty)}$ (ng h/mL)	C_{max} (ng/mL)	T_{max} (h)	56
			Marketed F	578.21± 18.45	65.67±61.41	2.14±0.21	
			Transdermal patch	1461.54± 76.34	54.19±14.67	8.57±1.98	
Glimepiride	Cholesterol, ethanol, Propylene glycol, Hydroxypropyl methyl cellulose ethosomes (61 nm)	Transdermal, (1.76 cm^2), 1 mg	*PK parameters*	$AUC_{(0-\alpha)}$ (ng min/mL)	C_{max} (ng/mL)	T_{max} (h)	104
			Transdermal films with pure drug	215.71	21.53	4	
			Marketed formulation (Amaryl® tablet)	397.55	135.16	2.5	
			Ethosomal loaded transdermal films	1187.48	46.09	2.5	
			3-fold increase in total drug release				
Glibenclamide	Chitosan and poloxamer 188 nanocrystals in transdermal patch (TDP)	3mg, Transdermal	*PK parameters*	Drug permeation (µg/cm^2)	Cumulative drug release (µg/cm^2)		105
			Glibenclamide	107±4.3 (at 0.5 h) and	362±25.25		

	(429 nm)		loaded microcrystals	119±8.6 (at 1 h)			
			Glibenclamide loaded nanocrystal	148±5.43 (at 0.5 h) and 177±10.6 (at 1 h)	498±33.35		
			In diabetic rats: Hypoglycemic effect at 24h was significantly higher when compared with oral glibenclamide or glibenclamide loaded microcrystals TDP				
				$AUC_{(0-\infty)}$ (ng h/mL)	$t_{1/2}$ (h)	C_{max} (ng/mL)	T_{max} (h)
	NLC of Capryol™ 90 (120.69±2.13 nm)	1 mg, Transdermal	Oral suspension of marketed preparation (Daonil®)	3042.11 ±216.3	8.88 ±0.07	448.65±32.65	2.0± 0.28
			Glibenclamide conventional gel, 1mg	1166.54±120.42	13.66±1.21	98.96±15.16	4±1.62
			NLC	4141.61±265.32	17.33±1.1	265.63±18.96	4±0.91
Miscellaneous nanoformulations							
	Layersomes using poly(allylamine hydrochloride), poly(acrylic acid) and folic acid (266.2±10 nm and 25.4 mV)	50 IU/kg, Oral	The developed FA-Ins-layersomes exhibited: Excellent stability in simulated biological fluids and hypoglycemic response in diabetic rats. Prolonged hypoglycemia up to 18 h, indicative of easy-to-administer, patient-friendly oral formulation that can combat diabetes with improved therapeutic profile.				106
Insulin	Glucose responsive poly(ethylene glycol)-block-poly[(2-phenylboronic esters1,3-dioxane-5-ethyl) methylacrylate] (MPEG-block-PPBDEMA) micelles (50 nm and -40.2 mV)	--	The block polymers containing phenylborate ester that responded to changes in the glucose concentration at neutral pH and act as self-regulated insulin delivery				107
Metformin	Metformin conjugated	150	Prolong drug release, nanotubes-maintained hypoglycemia for a much longer				108

	carbon nanotubes	mg/kg, orally	time	
Repaglinide	Repaglinide-phospholipid complex enriched micelles using poloxamer 188 (525.79±23.62 nm)	2 mg/kg, for 7 days, orally	83.02% reduction in blood glucose level, by the optimized formulation, while only 55.40% reduction by marketed tablet (2mg/kg), orally for 7 days	38
Exenatide	Poly (ethylene glycol)-*b*-brush poly(l-lysine) polymer (24 nm)	5 µg/kg, s.c.	Blood glucose level maintained for 7 days, as compared to free drug solution (4.5h)	109, 110

at a dose of 3 mg/kg with a maximum of 300 mg intravenously (infusion) for 10 min for every 6 h till 31 days.[111] These studies and reports prove the immense therapeutic potential of LSF but also illustrate a difficult and patient non-compliant dosage regimen of LSF attributed to its short half-life and rapid clearance. Thus, orally active formulation of the drug if available could provide a major relief to patients with T1DM.

7. Drug-fatty acid conjugates and delivery systems

Oral drug delivery route is one of the most convenient and commonly used drug administration routes. But there are several drugs that exhibit poor bioavailability upon delivering them orally. One of the appropriate strategies used to address this problem is the use of drug-fatty acid conjugates. Drug-fatty acid conjugates are the drug molecules which have been covalently modified along with a fatty acids. Such conjugates have shown many benefits including enhanced oral bioavailability, improved tumor targeting, decreased toxicity and improved drug loading into delivery carriers.[112-114] Fatty acids consist of hydrocarbon chain and a reactive carboxylic acid group which have been conjugated with the drugs to make them hydrophobic. The fatty acids are used because of their characteristic properties such as biocompatibility, additional functional roles in drug targeting or self-assembly and chemical flexibility for modification. The widely used technique is to conjugate the carboxylic end of the fatty acid with a drug's hydroxyl or amine group to form a stable ester or amide linkage .[115] Many fatty acids and their derivatives were used for the development of conjugates (**Table 1.2)** and these conjugates have been delivered using different carriers including self-assembled systems (without carriers), liposomes, emulsions, lipid nanoparticles, micelles, and polymer NPs etc.

Table 1.2

Drug-fatty acid conjugates and their delivery systems.

S.No.	Fatty acid	Drug	Delivery system	Ref.
1	Conjugated linoleic acid	Paclitaxel	Liposome	116
2	Stearic acid	Gemcitabine	Polymer nanoparticle lipid nanoparticle, micelle	117,118,119
		5-fluorouracil	Lipid nanoparticle	120
3	Lauric acid	Cytarabine	Self-assembled nanofiber	121
4	Oleic acid	Docetaxel	Nanostructured lipid carrier	122
		Paclitaxel	Emulsion	123
		Imiquimod	Cream	124
5	Palmitic acid	Dexamethasone	Emulsion	125
		Paclitaxel	Emulsion	126
		Doxorubicin	Micelle	127
		TGX-221	Micelle	128
		siRNA	Polymer nanoparticle	129
		Capecitibane	Lipid nanoparticle	130
6	DHA	Doxorubicin	No carrier	131
		Paclitaxel	No carrier	132
		Lovastatin	No carrier	133
		10-hydroxycamptothecin	No carrier	134
7	Mystiric acid	Cabotegravir	Nanoparticles	135
8	Hexanoic acid, Octanoic acid, Decanoic acid, and Dodecanoic acid	Entecavir	No carrier	136
9	Octadecanoic acid	Gemcitabine	Nanoassembly	137

7.1. Lisofylline (LSF): suitable candidate for conjugate formation

LSF is a potent hydrophilic drug with reported benefit in T1DM and its aqueous solubility is approx. 60 mg/mL which makes it difficult to be formulated into any nano drug delivery system. Apart from solubility, major concern with LSF is its interconversion to its parent drug pentoxifylline (PTX).[138] Delivery of LSF by any conventional approach fails to solve the problems of drug metabolism and its poor PK parameters. Interconversion of LSF

and PTX is mainly attributed to free hydroxyl group found in LSF side chain which is gets oxidized in the presence of oxidoreductase enzymes (**Figure 1.1**). Considering this, conjugation of LSF with a hydrophobic moiety such as a fatty acid appears to be a preferable strategy that could consume the free hydroxyl group of LSF and further it could be delivered using a nano-formulation. Conjugation of LSF with hydrophobic moieties like polymer or fatty acids can impart hydrophobicity to LSF, the resulting conjugate can be encapsulated into any nano drug delivery system and can also reduce the excessive metabolism of LSF providing an overall enhanced efficacy.

8. Objectives of the present research and development endeavor

The objective of this work was to overcome the challenges associated with LSF by synthesizing LSF-fatty acid conjugate and to deliver it by a suitable nanoformulation for effective treatment of T1DM (**Figure 1.1**). The advantages of preparing a fatty acid conjugate of LSF are*, a) impart hydrophobicity to the drug to enable its efficient encapsulation into the delivery system and, b) reduce drug metabolism by protecting its hydroxyl group and thus prolonging its half-life.* Further, an oral delivery system for LSF-fatty acid conjugate nanoformulation was envisaged, developed and evaluated.

The specific goals of this research work are outlined below:

1. Analytical and bioanalytical method development and validation of LSF and PTX
2. Synthesis, characterization and evaluation of LSF-linoleic acid (LSF-LA) conjugate
    i. Synthesis and characterization of LSF-LA
    ii. Self-assembly of LSF-LA conjugate into micelles (LSF-LA SM)
    iii. *In-vitro* evaluation of LSF-LA SM in cell culture
    iv. Pharmacokinetics and *in-vivo* efficacy studies of LSF-LA SM in T1DM animal model

3. Development and evaluation of polymeric nanoformulation of LSF-LA conjugate
    i. Development of polymeric micelle formulation of LSF-LA (LSF-LA PLM)
    ii. *In-vitro* evaluation of LSF-LA PLM in cell culture
    iii. Pharmacokinetics and *in-vivo* efficacy studies of LSF-LA PLM in T1DM animal model
4. Designing of an oral tablet dosage form of LSF-LA PLM
    i. Scale-up and lyophilization of LSF-LA PLM
    ii. Preparation and characterization of LSF-LA PLM tablets
    iii. Pharmacokinetic studies of LSF-LA PLM tablets

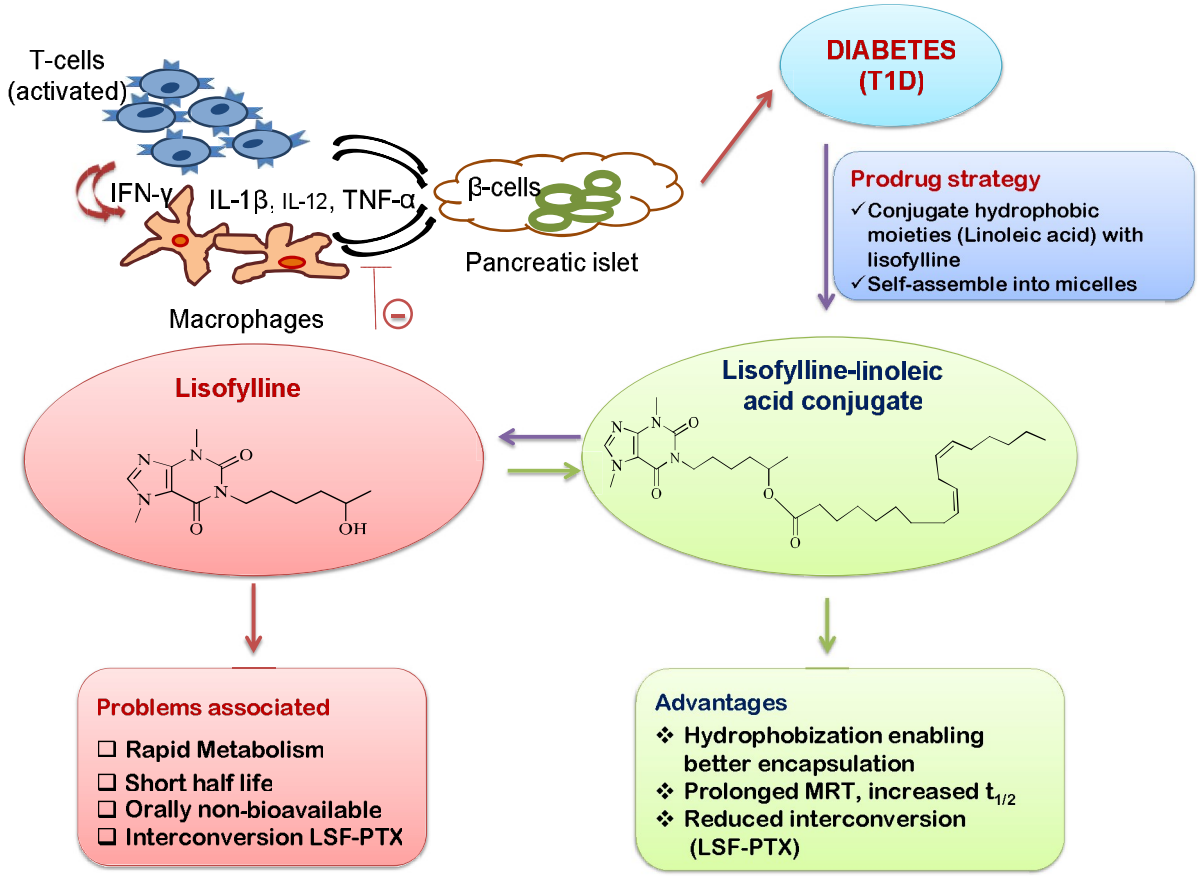

Figure 1.1 Mechanism of action of LSF in T1DM, problems associated with LSF and our proposed strategy and its advantages.

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