

Diabetes Mellitus: A Comprehensive Review On Pathophysiology, Current Therapeutic Challenges, And Future Perspectives Using PLGA Microspheres

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ABSTRACT

Objective: To provide a comprehensive evaluation of Diabetes Mellitus (DM), its underlying pathophysiology, limitations of existing therapeutic approaches, and to review the potential of Poly (lactic-co-glycolic acid) (PLGA)-based novel drug delivery systems for improving insulin therapy.

Significance: Diabetes is a rapidly escalating global burden, and current insulin and oral hypoglycaemic treatments are limited by rapid enzymatic degradation, variable bioavailability, and poor patient adherence due to frequent dosing. Advanced delivery systems such as PLGA-based platforms may overcome these drawbacks by enabling sustained, pulsatile, and glucose-responsive insulin release.

Methods: A systematic evaluation of recent literature was conducted focusing on PLGA-based delivery technologies, including multilayer microspheres, glucose-responsive systems, PEGylated carriers, and surface-modified nanocarriers. Studies examining pharmacokinetics, release mechanisms, and therapeutic outcomes were critically reviewed.

Results: Emerging PLGA-based formulations demonstrate the ability to achieve sustained, near zero-order release of insulin with significantly reduced degradation and extended circulation time. Glucose-responsive microspheres and advanced surface-engineered systems showed improved pharmacodynamic control, reduced dosing frequency, and better mimicry of physiological insulin secretion compared to conventional therapies.

Conclusions: PLGA-driven novel drug delivery systems offer a transformative approach for diabetes management, addressing the limitations of current insulin therapies. The reviewed evidence indicates strong potential for these technologies to enhance therapeutic efficacy, improve patient compliance, and pave the way for personalized long-term glucose regulation.

Keywords: Diabetes Mellitus, Insulin Delivery, PLGA Microspheres, Sustained Release, Nanoparticles, Glucose-responsive.

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INTRODUCTION

Diabetes is a chronic metabolic disorder in which the body is unable to regulate blood glucose levels properly, leading to persistent hyperglycemia (high blood sugar). This condition occurs due to either a deficiency in insulin

secretion (as in Type 1 diabetes), resistance to insulin action (as in Type 2 diabetes), or a combination of both. Diabetes mellitus affects over 538 million people globally, with projections reaching 784 million by 2045 (1). Insulin is a hormone produced by the β -cells of the pancreas that helps

glucose enter body cells for energy production. When insulin is insufficient or ineffective, glucose remains in the bloodstream instead of being used by cells, resulting in increased blood sugar levels. Prolonged hyperglycemia in diabetes can cause serious complications affecting the eyes, kidneys, nerves, heart, and blood vessels. Despite advancements, conventional insulin therapies face limitations such as poor bioavailability, unpredictable pharmacokinetics, and patient non-adherence due to frequent injections(2). Diabetes mellitus is not a singular condition; it encompasses a range of metabolic disorders characterized by hyper glycaemia, resulting from impairments in insulin secretion and/or insulin function. Prolonged exposure to elevated blood glucose levels can

lead to microvascular complications affecting the retina, kidneys, or peripheral tissues. Diabetes mellitus (DM) refers to a group of related conditions where the body is unable to effectively regulate blood sugar levels, specifically glucose. Table 1 provides a list of the clinical significance of the two primary forms of diabetes, type 1 and type 2(3).

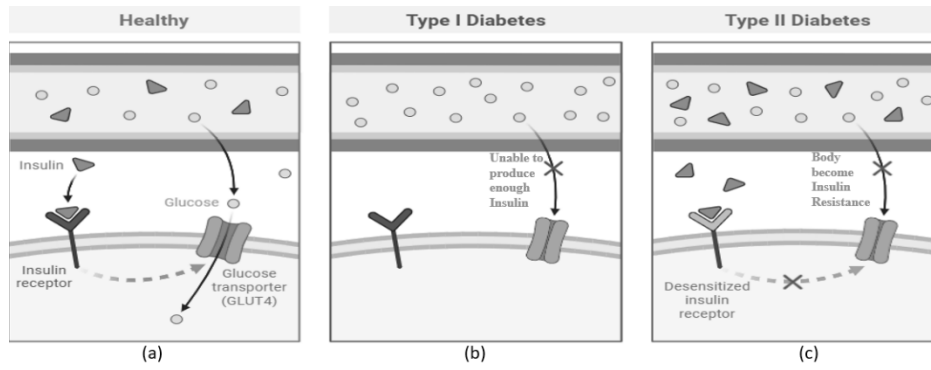
Pathophysiology And Classification

The disease is fundamentally characterized by chronic hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. Given below **Table 1.1** shows the Clinical and Pathogenic Distinctions Between Type I and Type II Diabetes Mellitus.

Table 1 : Clinical and Pathogenic Distinctions Between Type I and Type II Diabetes Mellitus(4).

Factor	Characteristic	Type I Diabetes	Type II Diabetes
Clinical	Onset	Typically, <18 years	Typically, >30 years
	Body Weight	Can occur in normal weight	Occurs mostly in obese persons
	Blood Insulin	Reduced	May be normal or increased
	Islet Cell Antibodies	Present	Absent (normal)
	Metabolic Acidosis	Common	Not common
Pathogenesis	Mechanism	Autoimmune destruction of β -cells, serious insulin deficiency	Insulin resistance with relative insulin deficiency.
Genetics	Concordance in Twins	~50%	65-80%
	HLA-D Linkage	Linked	Not linked
Islet Cells	Histology	Pancreatic inflammation (insulinitis), atrophy, fibrosis, β -cell depletion	No inflammation, mild atrophy and amyloid deposits, fewer β -cell depletion.

1.2 Types of Diabetes



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Figure 1 Showing the cellular mechanisms of glucose uptake in (a) healthy state (b)&(c) diabetes state.

Type 1 Diabetes

An autoimmune condition known as type 1 diabetes occurs when the pancreatic β -cells are unable to secrete enough insulin, a hormone that aids in the use of glucose (blood sugar) as fuel. There will be too much glucose in the blood and the cells will run out of energy(5). The potentially fatal disorders of hypoglycemia, or low blood sugar, and hyperglycaemia, or excess blood sugar, come next(6). Cells do not receive enough glucose when hypoglycemia occurs, and patients experience disorientation, unconsciousness, and coma. Long-term glucose deprivation in the brain can even cause death. Ketoacidosis, a buildup of ketones in the blood when the body utilizes fat for energy instead of glucose, can be brought on by hyperglycaemia and a prolonged lack of insulin. This is due to the fact that in steady state, fatty acids cannot be transformed into glucose. Ketones slow down every bodily function and turn the blood acidic. Additionally, this results in a coma and ultimately death(7). In the above Figure 1 it clearly shows the types of Diabetes.

Diabetes mellitus type 2 is a complicated metabolic and endocrine condition. A diverse and progressive illness with varying degrees of insulin resistance and pancreatic β -cell malfunction is the consequence of the interplay of several hereditary and environmental variables. One of the main causes of insulin resistance and decreased glucose tolerance is being overweight. Impaired glucose tolerance develops into type-2 diabetes when β cells are unable to release enough insulin to overcome insulin resistance(8).

CONVENTIONAL TREATMENT STRATEGIES

Current therapeutic management aims to maintain Glycated Haemoglobin (HbA1c) levels below 7% to minimize long-term complications. The pharmacological arsenal is divided into oral hypoglycaemic agents and injectable insulin therapies. Given below **Table 2** shows the conventional treatment available for the treatment of diabetes and their mechanism of action along with therapeutic benefits and their limitations.

Type 2 Diabetes

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Drug Class	Drugs	Mechanism of Action	Therapeutic Benefits	Limitations & Adverse Effects	Ref.
Biguanides	Metformin	Activates AMPK to reduce hepatic glucose production and improve insulin sensitivity.	First-line therapy; weight neutral; cardiovascular protection; low cost.	Lactic acidosis (rare); Vitamin B12 deficiency; GI disturbances (diarrhoea).	(9)
Sulfonylureas (2nd Gen)	Glimepiride, Gliclazide	Blocks K-ATP channels in pancreatic beta-cells, stimulating calcium influx and insulin secretion.	High potency in lowering HbA1c; rapid onset.	High risk of hypoglycaemia; weight gain; beta-cell exhaustion over time.	(10)

Meglitinides	Repaglinide, Nateglinide	Closes K-ATP channels (similar to sulfonylureas) but with a faster, shorter action.	Targets postprandial hyperglycaemia; flexible "skip meal, skip dose" dosing.	Frequent dosing (TID); hypoglycaemia risk; weight gain.	(11)
Thiazolidinediones (TZDs)	Pioglitazone, Rosiglitazone	PPAR-gamma agonist; increases insulin sensitivity in peripheral tissues (adipose/muscle).	Durable glycaemic control; improves lipid profile (HDL increase).	Fluid retention (edema); heart failure risk; bone fractures; bladder cancer risk.	(12)
alpha-Glucosidase Inhibitors	Acarbose, Voglibose	Reversibly inhibits intestinal alpha-glucosidase enzymes, delaying carbohydrate digestion.	Reduces post-meal glucose spikes without causing hypoglycaemia.	Severe GI effects (flatulence, bloating); frequent dosing; modest HbA1c reduction.	(13)
DPP-4 Inhibitors (Gliptins)	Sitagliptin, Linagliptin	Inhibits DPP-4 enzyme, preventing degradation of endogenous incretins (GLP-1, GIP).	Weight neutral; well-tolerated; safe in renal failure (Linagliptin).	High cost; modest efficacy; potential risk of pancreatitis and joint pain.	(14)
SGLT2 Inhibitors (Gliflozins)	Empagliflozin, Dapagliflozin	Blocks glucose reabsorption in the proximal renal tubule, promoting glycosuria.	Weight loss; reduces blood pressure; major heart failure & kidney benefits.	Genital mycotic infections; UTIs; risk of Diabetic Ketoacidosis (DKA); dehydration.	(15)
GLP-1 Receptor Agonists	Liraglutide, Semaglutide	Mimics GLP-1 to stimulate glucose-dependent insulin release and slow gastric emptying.	Significant weight loss; cardiovascular protection; potent HbA1c reduction.	GI toxicity (nausea/vomiting); injectable (mostly); risk of thyroid C-cell tumours (rodents).	(16)
Dual GIP/GLP-1 Agonists (Twincretins)	Tirzepatide	Activates both GIP and GLP-1 receptors synergistically for superior glycaemic control.	Unmatched weight loss (up to 20%); superior HbA1c reduction vs. GLP-1 alone.	GI side effects (nausea, diarrhoea); expensive; injectable only.	(17)
Amylin Analogs	Pramlintide	Synthetic analog of amylin; slows gastric emptying and suppresses glucagon.	Approved for Type 1 & Type 2; promotes weight loss.	Severe nausea; increased hypoglycaemia risk when used with insulin; injectable.	(18)
Bile Acid Sequestrants	Colesevelam	Binds bile acids in the intestine; exact mechanism in diabetes is unclear (likely FXR mediated).	Lowers LDL cholesterol; non-systemic (safe for liver/kidney disease).	Constipation; dyspepsia; increases triglyceride levels; high pill burden.	(19)
Dopamine-2 Agonists	Bromocriptine (QR)	Modulates hypothalamic dopamine activity to reset circadian glucose rhythms.	Cardiovascular safety; no hypoglycaemia.	Nausea; fatigue; dizziness (orthostatic hypotension); modest efficacy.	(20)

Oral Hypoglycaemic Agents

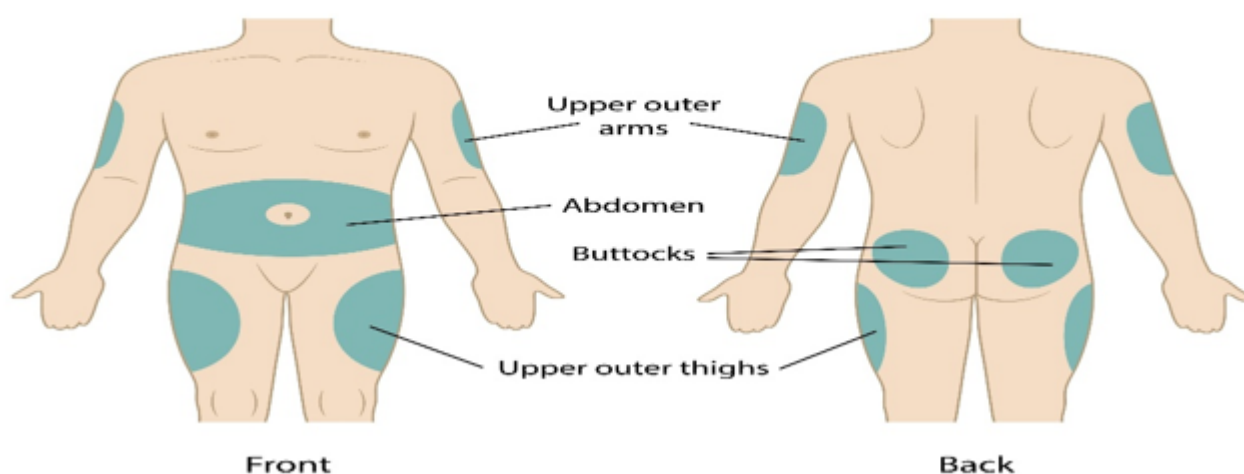
For T2DM, first-line therapy typically involves Biguanides (e.g., Metformin), which suppress hepatic gluconeogenesis. Other classes include Sulfonylureas, which stimulate insulin secretion, and newer agents like SGLT2 inhibitors and DPP-4 inhibitors that offer cardiovascular benefits. However, each class has distinct limitations, such as the risk of hypoglycaemia with Sulfonylureas or gastrointestinal side effects with Metformin.(21)

2.1 Insulin Therapy

The administration of exogenous insulin serves as the foundational pillar of management for all individuals with Type 1 Diabetes Mellitus (T1DM), necessitated by the irreversible loss of pancreatic beta-cell function. Furthermore, insulin therapy is frequently imperative for patients with Type 2 Diabetes Mellitus (T2DM) who exhibit

severe symptomatic hyperglycaemia or for whom oral pharmacological interventions have proven insufficient the central goal of contemporary insulin regimens is to replicate the natural pulsatile secretion pattern of the healthy pancreas, which involves a steady baseline release punctuated by rapid surges following nutrient ingestion.(22,23) To approximate this physiological profile, the prevailing clinical standard involves the "Basal-Bolus" approach, which utilizes two distinct categories of insulin analogs. Basal insulin formulations (such as Insulin Glargine, Detemir, or Degludec) are typically injected once or twice daily to inhibit hepatic glucose output and regulate fasting glycaemic levels.(24) These long-acting agents are chemically modified to precipitate subcutaneously or bind to albumin, ensuring a prolonged, consistent absorption profile without

Insulin injection sites



significant peaks Conversely, Prandial (Bolus) insulin (including Insulin Lispro, Aspart, or Glulisine) is administered immediately prior to meals.(25) These rapid-acting analogs serve to blunt postprandial glucose spikes by rapidly dissociating into monomers for quick systemic absorption Despite the clinical efficacy of this regimen, the requirement for parenteral administration—driven by the vulnerability of insulin to gastric enzymatic degradation remains a substantial hurdle to optimal patient adherence.(26)

2.2 Limitations of Current Therapies

Despite the availability of potent pharmacological interventions, attaining optimal glycaemic targets remains an elusive goal for a substantial patient demographic. The major impediments associated with conventional therapeutic regimens include.

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Figure 2 Showing the site for Insulin Injection(27)

The majority of protein-based therapeutics, including insulin and GLP-1 receptor agonists (e.g., Liraglutide), are susceptible to proteolytic degradation within the gastrointestinal tract, thereby mandating parenteral delivery. The necessity for repeated subcutaneous injections often precipitates needle phobia, injection site pain, and localized lipodystrophy, all of which contribute significantly to suboptimal patient adherence.(28)

2. Hypoglycaemic Episodes:

Exogenous insulin delivery systems lack the precision to perfectly match real-time physiological requirements. In scenarios of accidental overdose or missed meals, there is a heightened risk of severe hypoglycaemia (blood glucose < 70 mg/dL), a critical condition that can progress to

neuroglycopenia, loss of consciousness, or fatal outcomes.(29)

3. Pharmacokinetic Instability:

Most conventional insulin formulations exhibit a relatively short half-life, resulting in fluctuating plasma drug concentrations. This "peak and trough" phenomenon necessitates frequent dosing intervals to sustain therapeutic efficacy, imposing a considerable burden on the patient's daily life.(30)

4. Absence of Bio-Feedback:

Unlike the functional pancreas, traditional injection therapies operate as "open-loop" systems that are incapable of auto-regulating in response to glycaemic fluctuations.

Consequently, they cannot autonomously adjust dosage to counteract sudden hyperglycemic spikes or hypoglycaemic drops.(31)These critical shortcomings underscore the urgent necessity for the development of **Novel Drug Delivery Systems (NDDS)**, particularly PLGA-based microsphere technologies, which offer the dual advantages of sustained release kinetics and intelligent, glucose-responsive modulation.

RECENT ADVANCEMENT

Recent literature highlights significant strides in improving encapsulation efficiency and release kinetics. Given below **Table 3** showing the Recent Advancement in the treatment of Diabetes.

Table 3 Recent Advancement in the treatment of Diabetes

S. No.	Approach	Formulation	Key Findings	Reference
1.	Porous Architecture	Porous PLGA microspheres using ammonium bicarbonate as a porogen.	Created an internal honeycomb structure that increased drug loading by 300% and reduced the initial "burst release" compared to solid microspheres.	(32,33)
2.	Nanoprecipitation	Insulin-loaded PLGA nanoparticles with PEG surface modification (PEGylation).	PEG coating evaded the immune system (stealth effect), prolonging circulation time and maintaining normoglycemia for 24 hours in diabetic rats.	(34)
3.	Smart Gating	Glucose-responsive PLGA microspheres containing Phenylboronic Acid (PBA).	Demonstrated a "pulsatile" release profile; insulin release increased 5-fold in hyperglycaemic conditions compared to normal glucose levels.	(35)
4.	Composite Hydrogels	PLGA microspheres embedded in a thermosensitive hydrogel (PLGA-PEG-PLGA).	The system is liquid at room temperature but gels at body temperature (37°C), forming a depot that provided sustained release for 14 days.	(36)
5.	Oral Delivery	PLGA nanoparticles coated with Chitosan (Mucoadhesive).	Chitosan coating opened tight junctions in the intestine, increasing oral bioavailability of insulin to 10.5% (significant for oral route).	(37,38)
6.	Micro-Plates	Geometry-controlled PLGA "Microplates" (non-spherical).	The unique flat shape prevented phagocytosis by immune cells and allowed for faster response times to glucose spikes than spheres.	(39)
7.	pH-Response	Eudragit-coated PLGA nanoparticles.	The pH-sensitive coating protected insulin from acidic gastric fluid (pH 1.2) but dissolved in the intestine (pH 7.4), enabling targeted release.	(40)
8.	Co-Delivery	PLGA microspheres co-encapsulating Insulin and Quercetin (Antioxidant).	Co-delivery reduced oxidative stress at the injection site and improved the stability of the encapsulated insulin during storage.	(41)
9.	Inhalable Carriers	Large Porous Microparticles (LPM) via spray drying.	Low-density particles with aerodynamic diameter <5 µm achieved deep lung deposition, offering a non-invasive alternative to injections.	(42)

10.	Zwitterionic Coating	PLGA nanoparticles with super-hydrophilic zwitterionic coating.	The coating allowed particles to penetrate the intestinal mucus barrier effortlessly, significantly enhancing oral absorption efficiency.	(43,44)
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MODERN APPROACHES: THE FUTURE OF DELIVERY

To address the shortcomings of conventional injections, research has shifted toward Novel Drug Delivery Systems (NDDS) that provide sustained release. Poly (lactic-co-glycolic acid) (PLGA) has emerged as the polymer of choice for these advanced formulations. PLGA is a biocompatible and biodegradable copolymer approved by the FDA for human use. Its primary advantage lies in its safety profile; it degrades within the body into non-toxic byproducts—lactic acid and glycolic acid—which are naturally eliminated via the Krebs cycle.(45)

Biocompatibility & Safety: PLGA is approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for parenteral use. Its safety profile is superior because it undergoes non-enzymatic hydrolysis in the body to form non-toxic metabolic byproducts—lactic acid and glycolic acid—which are subsequently eliminated via the Krebs cycle as carbon dioxide and water.(46)

Tunable Degradation: The release rate of the encapsulated insulin can be precisely engineered by altering the ratio of

Lactide to Glycolide (L:G ratio). For instance, a 50:50 ratio degrades faster (weeks), while a 75:25 ratio degrades slower (months), allowing formulation scientists to design depots that last for specific durations.(47)

Protection of Payload: The polymeric matrix acts as a physical shield, protecting the fragile insulin protein from premature enzymatic degradation by proteases at the injection site.

GLOBAL CLINICAL LANDSCAPE AND PATENT OVERVIEW

The transition of PLGA-based insulin delivery systems from bench to bedside is evidenced by numerous ongoing clinical trials and patent filings. This section highlights key global studies (Phase 1–3) and innovative patents from 2020–2025, demonstrating the industry's shift toward once-weekly injectables, oral insulin capsules, and smart glucose-responsive technologies. Given below Table 4: Global clinical trials and key patents regarding modern insulin delivery systems and glucose-responsive therapies.

Table 4: Global clinical trials and key patents regarding modern insulin delivery systems and glucose-responsive therapies (2020–2025).

S. No.	Therapy / Innovation	Trial ID / Patent No.	Stage	Inference / Therapeutic Potential	Reference
1.	Insulin Icodec (Awiqli)	NCT04466267 (ONWARDS 1)	Phase 3 (Completed/ Approved in EU)	A once-weekly basal insulin analog. The trial demonstrated that weekly Icodec is non-inferior to daily Glargine in HbA1c reduction, improving patient adherence significantly.	(48)
2.	Insulin Efsitora Alfa	NCT05463744 (QWINT-2)	Phase 3 (Ongoing)	A weekly basal insulin fusion protein (IgG-Fc). Early results indicate stable glycemic control with a flat pharmacokinetic profile, challenging daily injections.	(49)
3.	Glucose-Sensitive Insulin (NNC2215)	NCT05342623	Phase 1	A novel "Smart Insulin" engineered to activate only when blood glucose is high. This represents the first clinical step toward a "hypoglycaemia-proof" insulin.	(50)

4.	Oral Insulin Capsule (ORMD-0801)	NCT03430856	Phase 3 (Completed)	An oral capsule using intestinal permeation enhancers. While efficacy was mixed, it validated the concept that oral delivery can survive gastric pH.	(51)
5.	VX-880 (Stem Cell Therapy)	NCT04786262	Phase 1/2	Allogeneic stem cell-derived islet cells. The therapy successfully restored endogenous insulin production in T1DM patients, reducing or eliminating the need for exogenous insulin.	(52)
6.	Glucose-Responsive Microgels	Patent: US10517830B2 (MIT/Zhen Gu)	Preclinical	Describes a polymeric microgel containing phenylboronic acid (PBA). The patent claims a rapid "expansion-release" mechanism that releases insulin within minutes of a glucose spike.	(53)
7.	Tirzepatide (Twincretin)	NCT04184606 (SURPASS-1)	Phase 3 (Approved)	First-in-class dual GIP/GLP-1 receptor agonist. Demonstrated superior weight loss and glycaemic control compared to Semaglutide, setting a new benchmark for T2DM treatment.	(54)
8.	PLGA-PEG Nanocarriers	Patent: CN112603768A	Preclinical	A formulation patent for long-circulating PLGA-PEG nanoparticles. The innovation lies in the specific surface modification that extends plasma half-life to >24 hours.	(55)
9.	Once-Weekly Semaglutide (Oral)	NCT03693430 (PIONEER PLUS)	Phase 3	Investigating high-dose oral Semaglutide. If successful, this could replace injectable GLP-1 agonists entirely, shifting the market to oral tablets.	(56)

CONCLUSION

The management of Diabetes Mellitus has evolved significantly from standard insulin replacement to sophisticated formulation strategies; however, the limitations of conventional therapy—specifically invasive administration, hypoglycaemic risks, and poor patient adherence—remain critical barriers to optimal care. This review highlights that PLGA-based Novel Drug Delivery Systems (NDDS) represent a transformative solution to these challenges. By leveraging the biocompatibility and tunable degradation kinetics of PLGA, researchers have successfully engineered microspheres that offer sustained, zero-order insulin release, effectively mitigating the "peak and trough" plasma profiles associated with daily injections. Furthermore, the integration of "smart" technologies, such as Phenylboronic Acid (PBA)-based glucose sensing, has paved the way for closed-loop delivery systems that mimic the physiological function of a healthy pancreas. While preclinical data is highly promising, the transition from laboratory prototypes to clinical reality requires addressing challenges in large-scale manufacturing, sterilization

stability, and regulatory approval for complex generics. Nevertheless, the ongoing progress in weekly injectables and oral delivery platforms suggests a paradigm shift is imminent. The future of diabetes management lies in these personalized, non-invasive delivery systems, which promise not only to improve glycaemic control but, more importantly, to significantly enhance the quality of life for millions of patients worldwide.

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