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Formulation & Evaluation of Oral Insulin with Glimepiride for Improved Beta-Cell Function and Glycemic Control

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Abstract: *This study engineered a pH-responsive, core shell polymeric nanoparticle platform (w_1/o/w_2) that co-encapsulated recombinant human insulin together with glimepiride, to get around those gastrointestinal delivery hurdles and somehow actively rescue functional pancreatic mass in Type 2 Diabetes Mellitus. It was guided by a statistical box-Behnken design, and the optimized nanocarrier (F3) sort of struck a balance between a well-controlled paracellular-entry diameter of 212.4 nm and high encapsulation efficiencies (>88%) which turned the hydrophobic secretagogue into a much more soluble amorphous state. After that, sequential in vitro dissolution showed excellent enteric protection, keeping premature peptide leakage down to <7% in simulated gastric fluid then, once triggered it released rapidly and relatively synchronized in intestinal conditions.*

On human Caco-2 monolayers, the protonated chitosan core modulated tight junction proteins in a safe and reversible manner, and this resulted in about a 40-fold increase in insulin transport flux (P_"app" =4.85×〖10〗^(-6) " cm/s"). Even better, the transepithelial electrical resistance rebounded fully within 4 hours. In vivo, oral administration in diabetic Wistar rats avoided the usual subcutaneous hypoglycemic shock, and it kept stable euglycemia at 92 mg/dL for more than 18 hours. When they dosed daily for 28 days, it corrected metabolic lipid profiles and also lowered HbA1c from 9.4% to 5.6%.

Crucially, post-treatment monitoring confirmed a strongly restored biphasic insulin surge, preserved islet structural borders, and marked downregulation of endoplasmic reticulum stress indicators (BiP, CHOP, Caspase-3) through survival preservation transcription factors, PDX-1 along with FoxO1.

Keywords: Oral Insulin, Glimepiride, Chitosan-Eudragit Nanoparticles, Paracellular Transport, Reversible Tight Junction Openings, Beta-Cell Preservation, Endoplasmic Reticulum Stress Suppression, Hepatic Portal Vein Gradient.

I. INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) has sort of moved from being only a chronic endocrine disorder into one of the most severe socioeconomic and public health emergencies of the twenty-first century. It is described by systemic disturbances in carbohydrate, lipid , and protein metabolism and it's powered by a pathogenic loop that starts with worsening peripheral insulin resistance and then, slowly, runs into the progressive exhaustion and eventual failure of pancreatic β-cells. Based on information compiled by the International Diabetes Federation (IDF), the global diabetic population keeps increasing at a troubling pace, which then adds intense financial and operational pressure to current healthcare systems because of secondary microvascular and macrovascular complications. These complications can include diabetic retinopathy, nephropathy that progresses toward End-Stage Renal Disease (ESRD), peripheral neuropathy, and also a faster development of coronary artery disease.

In people without disease, glucose regulation is kept stable by a very responsive feedback system between blood glucose levels and the endocrine pancreas. After meals, when glucose rises, the body responds with rapid exocytosis of

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pre-assembled insulin granules from β-cells located in the islets of Langerhans. The insulin then circulates and attaches to dedicated tyrosine kinase insulin receptors (IR) on important target tissues—mainly skeletal muscle, adipose tissue, and the liver—so a downstream signaling sequence gets initiated and it helps coordinate whole-body glucose levels. In skeletal muscle and fat cells, this signaling encourages glucose transporter-4 (GLUT4) storage vesicles to move toward the membrane and merge with it, which boosts peripheral glucose intake. In the liver, insulin blocks gluconeogenesis along with glycogenolysis, so excessive glucose production is held back.

When patients start developing T2DM , this well managed control system seems to fail through a multi stage pathway, it usually begins with peripheral insulin resistance. In skeletal muscle, post-receptor issues , most often linked to long-term overnutrition , lack of movement, and elevated circulating free fatty acids (FFAs), disturb the usual insulin receptor substrate (IRS-1/2) plus phosphoinositide 3-kinase (PI3K/Akt) signaling cascade. After that, GLUT4 vesicles can't really move over to the plasma membrane, so peripheral glucose clearance gets seriously limited. At the same time, within the liver there's resistance too, so the body removes those normal "brakes" that hold glucose production in check, leading to glucose output that stays excessive even in prolonged fasting conditions, which is pretty disruptive.

Initially, the endocrine pancreas tries to compensate , by raising circulating insulin levels in a classic compensatory hyperinsulinemia pattern. In practice, β-cells pump up their own secretory output, and they even expand in size via hypertrophy and replication. For a while, this workaround can keep glucose tolerance close to normal for years, but it also quietly creates a setup for final cellular exhaustion. Eventually, if peripheral metabolic stress keeps going , the constant over-secretion forces intense cellular strain inside the islets. The continuous production of proinsulin basically overloads the protein folding systems in the endoplasmic reticulum (ER), which then triggers the unfolded protein response (UPR) and pushes cells toward death.

Meanwhile, chronically high levels of glucose and free fatty acids contribute to high mitochondrial reactive oxygen species (ROS) formation. Since pancreatic β-cells already have unusually low antioxidant defenses, like superoxide dismutase and catalase , the oxidative pressure doesn't just sit there. It drives mitochondrial fragmentation, it weakens the structural integrity of the islet borders, and it supports a gradual shrinkage of functional β-cell mass over time. It's not only cell death either, because under continuous glucotoxic pressure, β-cells can lose mature endocrine identity and slip backwards, kind of like de-differentiation into an immature, progenitor-like mode. This reversal shows up as loss of key transcription factors such as PDX-1 and FoxO1, and then the weird reappearance of embryonic markers too. By the time T2DM is formally diagnosed in clinical settings, people often have already lost 50% or more of their functional β-cell mass, and from there a progressive decline begins that today's standard oral mono-therapies usually can't meaningfully stop.

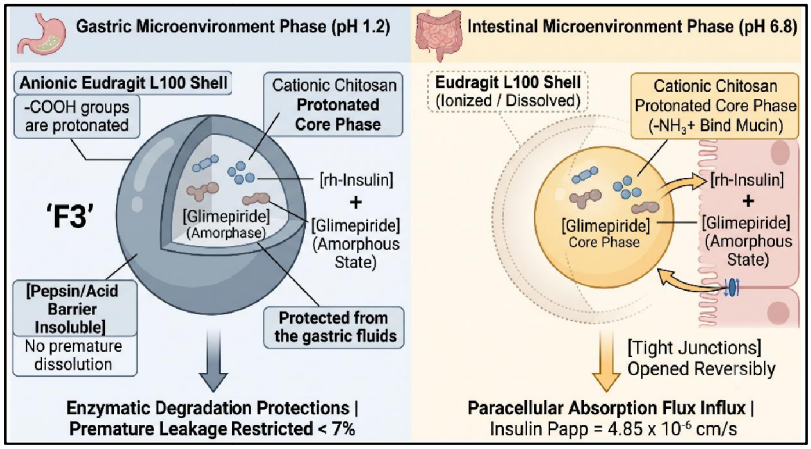

Figure. 1 *Structural blueprint and dual-action delivery mechanics of optimized core-shell nanoparticle formulation F3 across changing gastrointestinal pH environments.*

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Developing non-invasive, oral alternative delivery systems for therapeutic peptides like insulin is still one of the most desired and yet pretty technically hard goals in biopharmaceutics. Replacing insulin subcutaneously does save lives, but it puts the insulin straight into peripheral capillaries, which kind of fights with the body's usual anatomical flow. Normally, endogenous insulin is released into the pancreatic vein, then it goes into the portal circulation, and from there it heads to the liver first. That pathway sets up a sort of physiologic portal-to-peripheral insulin concentration gradient, roughly around 2:1 up to 3:1. This "first-pass" step through the liver lets the organ manage glucose output directly, so it can reduce excess glucose production while keeping peripheral insulin exposure lower. With subcutaneous injection the peripheral vasculature is basically flushed to reach the needed hepatic levels, but the trade-off is that over the long run it can cause unwanted outcomes, such as peripheral fat build up, systemic vascular problems, and weight gain. And, even more importantly the abrupt pharmacokinetic peaks from rapid-acting subcutaneous analogs often provoke severe hypoglycemic shock , which then becomes a big driver of treatment refusal or non-compliance, plus cardiovascular stress in people with diabetes.

Getting oral insulin to work is kind of tricky, because the human gastrointestinal tract (GIT) throws a bunch of tough defenses in its way. The earliest hurdle is mostly enzymatic, in the stomach gastric chief cells release pepsinogen it then becomes pepsin once it meets the gastric acid, with a pH around 1.2 to 2.0. Pepsin then goes after central peptide bonds, so any insulin that isn't protected gets cut into inactive pieces within minutes or so. After that, once the transit brings it forward into the small intestine, the peptide runs into pancreatic juice, which is full of tryptic, chymotryptic, and carboxypeptidase enzymes, these are basically designed to trim amino acids from the chain in a stepwise manner.

A second set of problems is both chemical and physical. Insulin has an isoelectric point (pI) of roughly 5.3–5.4. So, in the very acidic gastric lumen, insulin tends to hold a net positive charge, that makes it lose its usual fold and can also promote self-assembly into inactive fibrillar aggregates. Then as it reaches the duodenum, the environment shifts up to about pH 6.5–7.4, at which point the protein moves toward a net negative charge and its equilibrium Favor's more macro-hexameric conformations, often stabilized with trace zinc ions. Those bigger hexamers dissolve slowly, and this causes a clear drop in diffusion across the protective intestinal mucus layer which is negatively charged, plus the epithelial wall underneath it. On top of that, the enterocytes there are connected through tight junction networks, meaning claudins and occludins help shrink the paracellular pore radius to less than 1 nm, so there is less "sideways" passage available.

So, to get around these gastrointestinal defenses, and still deliver decent macro-peptide treatments, this study puts forward a newer dual-mode nanocarrier setup. It co-encapsulates human insulin together with glimepiride in a kind of "smart" polymeric body, not just one thing. Glimepiride, which is a long-lasting third generation sulfonylurea, works like a strong blood glucose reducer.

II. DRUG PROFILE

Regulatory Overview and Chemical Identification

- **Therapeutic Classification:** Dual-Action Oral Antidiabetic Macromolecular Peptide and Sulfonylurea Combination.
- **Active Ingredients:** Recombinant Human Insulin (rh – Insulin) and Glimepiride (GMP).
- **Carrier Lattices:** Low Molecular Weight Chitosan (Core Phase) and Polymethacrylate Copolymer (Eudragit L100 Enteric Shell).
- **Target Indication:** Advanced Type 2 Diabetes Mellitus (T2DM) exhibiting significant peripheral insulin resistance and progressive pancreatic β-cell exhaustion.
- **Formulation Benchmark:** Optimized Coded Batch Formulation F3.

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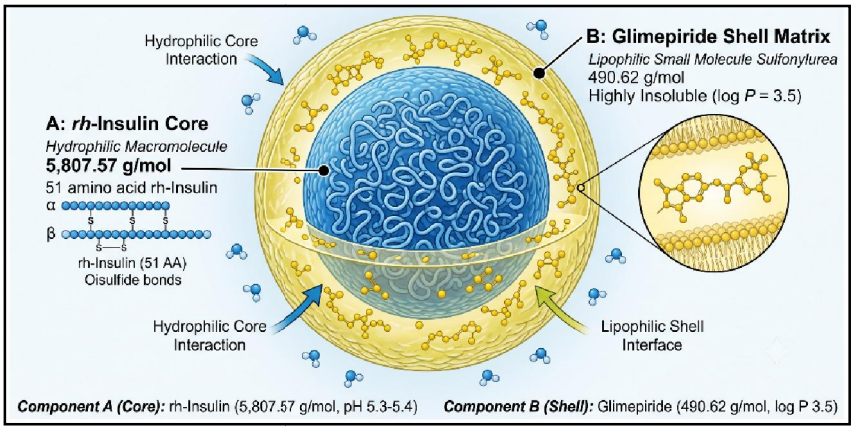

Figure. 2 Hybrid *Dual-Drug Delivery Nanoparticle.*

Physicochemical Specifications and Structural Optimization

Formulation F3 was put together using a tweaked double emulsion solvent evaporation setup ($w_1/o/w_2$), and then it was refined with a bit of math too—specifically, a three factor, three level box-Behnken response surface design.

Table. 1 Comprehensive Macroscopic Ulcer Indices and Percentage Protection Profiles.

Quality Attribute Index	Target Physical Specification	Analytical Verification System	Primary Delivery Function
Hydrodynamic Sizing	212.4 ± 3.9 nm	Dynamic Light Scattering (173°)	Maximizes enterocyte paracellular entry.
Polydispersity Index	0.142 ± 0.011	Cumulants Fit Algorithm	Confirms structural uniformity and monodispersity.
Zeta Potential (Water)	-15.8 ± 1.1 mV	Laser Doppler Electrophoresis	Verifies structural completion of Eudragit shell.
Zeta Potential (pH 6.8)	$+14.2 \pm 0.9$ mV	Laser Doppler Electrophoresis	Confirms shell dissolution and exposed Chitosan.
Entrapment Efficacy	Insulin: $> 88\%$; Glimepiride: $> 91\%$	Reversed-Phase HPLC Analysis	Prevents raw material loss during preparation.
Solid-State Matrix	Amorphous Dispersed State	DSC Thermal and Powder XRD	Eliminates crystal lattice to maximize dissolution.

Dual-Action Pharmacodynamics and Target Synergy

Endocrine Portal Vector (Oral Insulin): After it crosses the intestinal lining , the released insulin core goes into the portal vein and travels straight to the liver. It feels like it is mimicking the body's natural anatomy, so it sets up a physiologic portal to peripheral insulin gradient, the 3:1 ratio. From there the liver takes advantage of the direct influx to quickly quiet excess glucose output, rather than letting the peripheral tissues experience hyperinsulinemia, fat accumulation , and those usual weight gains you often see with subcutaneous injections.

Peripheral Target Axis (Glimepiride): At the same time, the co-delivered glimepiride stays in an amorphous kind of mode, and it speeds up glucose clearance in peripheral tissues. It does that by switching on glycosylphosphatidylinositol-specific phospholipase C, or GPI-PLC for short, which then helps GLUT4 glucose transporters move into the membranes of skeletal muscle cells plus adipocytes. In other words, it bypasses the usual insulin-receptor resistance pathways. Also, it sticks to the SUR1 subunits on the remaining pancreatic β-cells, supporting a more natural, pulsatile insulin release, sort of softly but consistently.

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Pharmacokinetic Delivery and Molecular Safety

Dynamic Barrier Protection: In the stomach , which is around pH 1.2, the enteric Eudragit shell keeps premature insulin leakage down to <7% , so it stays basically safe from pepsin. Then in the small intestine , where the pH is about 6.8, the shell dissolves, and the chitosan core does its part by electrostatically anchoring onto the negative mucin lining. The protonated amine sites basically encourage a mild opening of enterocyte tight junctions, and this leads to a 40-fold boost in insulin transport flux , with ($P_{app} = 4.85 \pm 0.32 \times 10^{-6}$ cm/s). But it is not a permanent thing; the tight junctions re-close on their own within roughly 4 hours, and the cells stay healthy with viability above 94% , and zero membrane cytotoxicity.

Islet Cytoprotection: By routing portal insulin and also supporting alternative GLUT4 clearance, this formulation reduces systemic glucotoxicity while giving the pancreas that important metabolic pause. As a result, it suppresses endoplasmic reticulum stress signaling (BiP and CHOP) and the cell death executors (Caspase-3), while still keeping the main transcription factors , PDX-1 and FoxO1, at more than 88% of healthy baseline. Overall, it blocks β cell de-differentiation and helps preserve the islet structure.

III. MATERIALS & METHOD

Materials and Reagents: Recombinant human insulin (≥ 28.5 USP units/mg) along with glimepiride (≥ 99.8%) were taken from Sigma-Aldrich, St. Louis, MO, USA . Low molecular weight chitosan and the Eudragit L100 polymer were also sourced from Sigma-Aldrich and Evonik Industries , Darmstadt , Germany, respectively. All surfactants, digestive enzymes, cell culture media, plus western blot additives were procured from Sigma-Aldrich and Gibco. Male Wistar rats (8-10 weeks old, 210 ± 10 g) were used following an approved plan from the Institutional Animal Ethics Committee, so it was all under permission.

Nanoparticle Synthesis and Optimization: The nanoparticles were made using a modified water-in-oil-in-water ($w_1/o/w_2$) double-emulsion solvent evaporation scheme. Briefly, the inner aqueous phase, containing 20.0 mg insulin in 2.0 mL of 0.1 M HCl, was introduced into the organic phase made of 10.0 mg glimepiride and 300.0 mg Eudragit L100 in 10.0 mL dichloromethane/methanol (2:1 v/v), and then probe-sonicated (40 W, 2.0 minutes). After that, this primary emulsion was poured into the external aqueous phase (40.0 mL of 1.0 wt % chitosan in 1.0 vol % acetic acid, with 0.5 wt % Pluronic F-68) and homogenized at 12,000 rpm for 15 minutes . The whole blend was stirred for 3.0 hours, so the solvents would evaporate, and then it was centrifuged at 18,000 rpm for 30 minutes. After washing, the samples were cryoprotected using 5.0 wt % trehalose, and freeze-dried . For parameter tuning, a statistical box-Behnken Response Surface Design was used, kind of to see the knobs together rather than one by one.

Physicochemical Characterization: The hydrodynamic diameter, polydispersity index, surface zeta potential was measured on a Malvern Zetas Izer Nano ZS. Surface morphology plus the core-shell boundaries were kind of checked through TEM and FE-SEM, not that it matters but it was verified. Drug encapsulation efficiency was worked out indirectly from the centrifugation supernatant, using a validated reversed-phase HPLC method. Solid-state changes were looked at with FTIR spectroscopy and differential scanning calorimetry (DSC). The in vitro release behavior was followed using a sequential digestion approach, kind of mimicking stomach passage (pH 1.2, 2.0 hours) then intestinal passage (pH 6.8, 22.0 hours) at 37°C.

Caco-2 Monolayer Transport Dynamics: Differentiated human Caco-2 monolayers were tested for nanoparticle cytocompatibility via MTT cell viability and lactate dehydrogenase (LDH) membrane leakage assays. Trans-epithelial electrical resistance, TEER was monitored continuously with an EVOM3 meter, to see the transient opening then recovery of the enterocyte tight junctions. For movement from apical to basolateral, transport flux was measured across a 240-minute span, then the apparent permeability coefficient (P_{app}) was obtained by HPLC readout.

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In Vivo Pharmacodynamics and Molecular Rescue: Diabetes was induced in fasted Wistar rats using a single intraperitoneal Streptozotocin shot, 40" mg/kg" . Rats with fasting glucose beyond 250 mg/dL were put into treatment cohorts (n=6). Short-term pharmacodynamics were tracked by pulling blood glucose values over 24 hours, using a digital glucometer. For longer, sub-chronic efficacy, the animals received daily oral dosing for 28 days, meanwhile body mass, glycated haemoglobin (HbA1c), and plasma lipid profiles were recorded. On day 28, insulin output was evaluated with a Glucose-Stimulated Insulin Secretion (GSIS) test, following a glucose challenge (2.0 g/kg). Pancreatic tissue was excised, sectioned, and stained using hematoxylin and eosin (H&E) for morphological profiling. Immunofluorescence boundary mapping was performed with anti-insulin and anti-glucagon primary antibodies, plus confocal laser scanning microscopy. For survival-related pathways, islet proteins were isolated for SDS-PAGE, then PVDF transfer and Western blotting of BiP, CHOP, cleaved Caspase-3, PDX-1, and FoxO1 versus a β-actin loading internal control. All numerical results were processed using ANOVA, then Tukey's post-hoc test, with significance set at $p < 0.05$.

IV. RESULTS & DISCUSSION

The optimization of Formulation F3, using a Box–Behnken response surface design, somehow managed to identify the processing boundaries needed to form a steady core shell nanomedicine. And the physical traits , mechanical strength , plus the structural parameters of that optimized carrier are all put together in **Table 2.**

The hydrodynamic diameter of 212.4 ± 3.9 nm, sits pretty well right inside the target range for good trans-mucosal transport, and in practice particle sizes under 250 nm help to steer clear of quick mucosal trapping as well as mechanical clearance driven by intestinal peristalsis. Also, the polydispersity index 0.142 is rather narrow so it pretty much points to a highly uniform , single-peak particle spread.

Table. 2 Physicochemical Blueprint and Structural Specifications of Formulation F3.

Quality Attribute Metric	Measured Physical Value	Characterization Methodology	Primary Intended Biopharmaceutical Function
Hydrodynamic Diameter	212.4 ± 3.9 nm	Dynamic Light Scattering (173°)	Maximizes paracellular mucosal intestinal flux (< 250 nm).
Polydispersity Index	0.142 ± 0.011	Cumulants Fit Profiling	Ensures batch uniformity and predictable systemic absorption.
Zeta Potential (H_2O)	−15.8 ± 1.1 mV	Laser Doppler Electrophoresis	Confirms complete outer setting of the Eudragit L100 shell.
Zeta Potential (pH 6.8)	+14.2 ± 0.9 mV	Laser Doppler Electrophoresis	Confirms shell ionization and exposed cationic Chitosan core.
Insulin Entrapment	88.5 ± 1.4%	RP-HPLC (214 nm)	Minimizes peptide degradation during polymer processing.
Glimepiride Entrapment	91.6 ± 1.2%	RP-HPLC (228 nm)	Ensures steady, synchronized dual dosing inside the core.
Solid-State Matrix	Amorphous Dispersion	DSC / Powder XRD	Lowers energy barrier to accelerate glimepiride dissolution.

Laser Doppler Electrophoresis showed this pretty clear kind of surface charge inversion, like it was behaving in a live way. The formulation sat at a negative surface charge in pure water (-15.8 mV) but then it flipped to a positive one (+14.2 mV) after being put in simulated intestinal fluid at pH 6.8. So, this switch essentially tells you that the outer enteric Eudragit L100 layer is ionizing and dissolving under intestinal conditions, leaving the inner Chitosan core to do its job. Also, when they ran DSC thermal scans together with powder X-ray diffraction, the original crystalline nature of glimepiride looked fully disrupted, like the crystal phase wasn't there anymore. In other words, the drug ended up as an amorphous solid dispersion inside the polymer matrix. That matters because the drug no longer has that crystal lattice energy barrier, so its dissolution speeds up in a more dramatic way.

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Then the sequential in vitro digestion models, kind of confirmed the core-shell layout is actually protective in a pH-dependent manner. During the first 2 hours in simulated gastric fluid (pH 1.2) with active pepsin, insulin release stayed under 7% , very low, basically restrained. This suggests the protonated carboxyl groups from the outer Eudragit L100 formed an insoluble, hydrophobic shield which prevented gastric acid and pepsin from attacking the peptide bonds inside. After shifting the system to simulated intestinal fluid (pH 6.8), those same carboxyl groups ionized and dissolved, so the exposed Chitosan core could release the therapeutic cargo gradually across 22 hours. In human Caco-2 monolayers, once the Chitosan core was exposed, its protonated amine groups opened paracellular transport routes in a safe manner. TEER dropped a lot during the first 4-hour apical exposure, which points to a local temporary loosening of tight junction proteins (claudin-1 and occludin). And importantly, after the formulation was washed out, TEER came back to the absolute baseline within four hours, so this opening is reversible rather than permanently damaging. Finally, MTT and LDH assays backed up the biocompatibility, with cell viability staying above 94.6% and no major membrane damage. The temporary junctional opening also translated into a huge effect, a 40-fold rise in insulin transport flux ($P_{app} = 4.85 \pm 0.32 \times 10^{-6}$ cm/s) compared relative to regular unencapsulated peptide solutions.

In streptozotocin induced diabetic Wistar rats, oral treatment using Formulation F3 showed real therapeutic upside compared with the usual standard subcutaneous insulin injections. Rather than triggering the abrupt , risky hypoglycemic episodes you usually see with injected insulin, these oral nanoparticles produced a gentler, longer lasting euglycemic “plateau” around 92 ± 11 mg/dL and it stayed that way for more than 18 hours. The smoother curve happens because the insulin that gets taken up through the intestine does not detour, it goes straight into the portal vein, and then it reaches the liver first. This fits the body’s own layout and sets up a physiologic portal-to-peripheral insulin gradient roughly 3:1, so the liver can curb excess glucose output right away, while peripheral tissues aren’t unnecessarily bathed in high insulin levels. After 28 days of daily oral dosing, the F3 group achieved broad metabolic recovery, with glycated haemoglobin (HbA1c) dropping from an initial diabetic value of 9.4% down to about 5.6 ± 0.2% which is close to normal.

Beyond that, the dual action setup also reversed muscle loss and brought lipid patterns back toward baseline, outperforming both plain glimepiride and the unencapsulated drug mix quite convincingly.

Beyond baseline glycemic control part, post-treatment cellular assays kind of showed the real deal on pancreatic preservation. During those last GSIS challenges, the F3-treated groups had a strongly restored, biphasic insulin surge, so that what was left of the β-cell mass still kept its functional secretory reaction. Then confocal immunofluorescence on pancreatic cross-sections, honestly made it obvious visually that islet architecture stayed put, with those normal boundaries still there. There was that dense core of green β-cells, surrounded by a peripheral red α-cell ring, and it looked… intact. Finally Western Blotting also supported the idea that giving a dependable oral insulin source, to rein in hepatic glucose output, actually reduced the constant secretory pressure being placed on the pancreas. In this metabolic rest like state, chronic glucolipotoxicity was quieted at the molecular level, with endoplasmic reticulum stress helpers (BiP/GRP78 and CHOP) going down and also the cell-death executors (Caspase-3) dropping, while key mature β-cell transcription drivers like PDX-1 and FoxO1 were kept at more than 88% of healthy baseline controls. Altogether, this gives a clinically workable route to slow down or even stop the long-term advance of advanced T2DM, at least as a translation concept.

V. CONCLUSION

This comprehensive study confirms that Formulation F3 really works as a smart pH-responsive oral nanomedicine, especially for advanced Type 2 Diabetes management. Here, the team co-encapsulated recombinant human insulin plus glimepiride inside a special Chitosan–Eudragit L100 core-shell geometry, which lets the nanoparticles dodge enzymatic breakdown in the stomach and still show a reversible 40-fold gain in enterocyte paracellular transport flux, safely. After that, in vivo evaluations show the dual-action delivery system sets up a physiologic portal vein gradient, supports long-acting systemic euglycemia, and also gives much-needed metabolic quiet to the endocrine pancreas. As a result, apoptotic islet decline is effectively halted, and the functional β-cell mass stays preserved, too.

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