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PEGYLATED PLGA NANOPARTICLES OF METFORMIN AND CURCUMIN: A PROMISING NANOTHERAPEUTIC APPROACH FOR DIABETIC NEPHROPATHY

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ABSTRACT

Diabetic kidney disease (DN) is a common complication of diabetes and a leading cause of chronic kidney disease worldwide. Long-term high blood sugar causes oxidative stress, inflammation, and scarring in the kidneys, which can lead to protein in the urine (albuminuria) and reduced kidney function.[1] Current treatments can slow diabetic kidney disease but cannot fully stop it, highlighting the need for new therapeutic approaches. Metformin, a first-choice diabetes drug, also protects the kidneys beyond lowering blood sugar. It activates AMPK, improves mitochondrial function, and reduces scarring and damage to kidney tubules.[2] Curcumin, a natural compound from turmeric (Curcuma longa), acts as an antioxidant and anti-inflammatory agent by blocking NF-κB signaling and activating the Nrf2/HO-1 protective pathways.[3] However, both drugs have low bioavailability and do not easily reach the kidneys. Recent studies show that nanoparticles can overcome these problems. PLGA nanoparticles coated with PEG are more stable, stay longer in the bloodstream, and can accumulate in the kidneys more effectively.[4] PLGA nanoparticles carrying metformin release the drug slowly over time and improve its absorption and circulation in the body.[5], PLGA nanoparticles carrying curcumin reduced cell death and scarring in kidney disease models of diabetes.[6] Co-delivery of metformin and curcumin in PEGylated PLGA nanoparticles has been suggested to produce synergistic effects by simultaneously modulating AMPK and Nrf2 pathways.[7] Future prospects include optimization of nanoparticle size and surface ligands for proximal tubule targeting, microfluidic scale-up for reproducible production, and comparative studies with standard DN therapies such as SGLT2 inhibitors and RAAS blockers. Preclinical evaluation and following clinical translation will be critical steps toward establishing PEGylated PLGA-based co-delivery of metformin and curcumin as a promising therapeutic option for DN.[8]

KEYWORDS: Diabetic kidney disease (DN), Nrf2/HO-1, AMPK, PEGylated.

INTRODUCTION

Diabetes mellitus (DM) is one of the fastest growing metabolic disorders worldwide, characterized by chronic hyperglycemia due to defects in insulin secretion, insulin action, or both.[9] According to the International Diabetes Federation, the global prevalence of diabetes is projected to reach 783 million by 2045.[10] Within the long-term complications of diabetes, diabetic nephropathy (DN) is one of the most severe and is a leading cause of end-stage renal disease (ESRD).[11] DN reports for nearly 30–40% of all cases of ESRD and enforces a significant healthcare burden due to the requirement of dialysis or kidney transplantation.[12]

The socio-economic burden is particularly high in developing countries, including India, where diabetes is highly prevalent but access to renal replacement therapy remains limited.[13] Hence, strategies aimed at early prevention and improved treatment of DN are urgently needed.

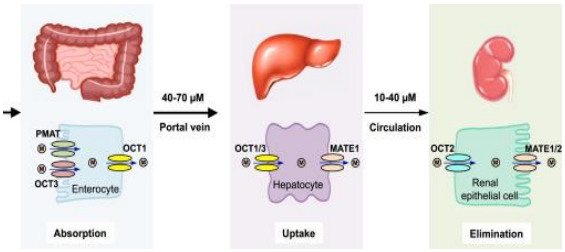

Fig. 1: After oral administration, metformin is absorbed by enterocytes in the intestine and delivered to the liver through the portal vein. Metformin concentrations in the portal vein are 40–70 µM. Metformin is not metabolized in hepatocytes, and is eliminated by the kidney unchanged. Metformin can also be secreted into bile through MATE1 transporter on hepatocytes.[2]

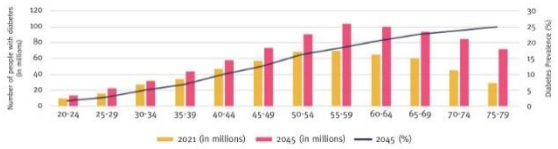

Fig. 2: Number of people with diabetes in adults (20–79 years) by age group in 2021 (columns) and estimated prevalence across age groups in 2045 (black line). Prevalence is standardised to each national population.[10]

Pathophysiology of Diabetic Nephropathy (DN)

The pathogenesis of DN is complex and multifactorial. Long-term high blood sugar causes changes in kidney metabolism and blood flow, which eventually lead to structural damage and impaired kidney function.[14]

• ***Hyperglycemia and Oxidative Stress:*** High blood sugar increases the production of harmful reactive oxygen species (ROS), mainly due to mitochondrial problems and the formation of advanced glycation end-products (AGEs).[15] ROS accumulation or deposition damages podocytes, mesangial cells, and tubular epithelial cells, leading to nephron injury.

• ***Inflammation:*** Hyperglycemia-induced oxidative stress activates multiple signaling pathways, including NF-κB and MAPK, resulting in the release of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6).[16] This promotes infiltration of macrophages and further increases renal damage.

• ***Fibrosis:*** Chronic inflammation stimulates the overexpression of profibrotic factors such as transforming growth factor-β (TGF-β), which induces extracellular matrix (ECM) accumulation and glomerulosclerosis.[17] Progressive fibrosis is a characteristics of DN, as a result it causes irreversible renal dysfunction.

Thus, the cascade or pathway of hyperglycemia leads to oxidative stress then occurs inflammation which results in fibrosis represents the primary mechanism underlying DN progression.[18]

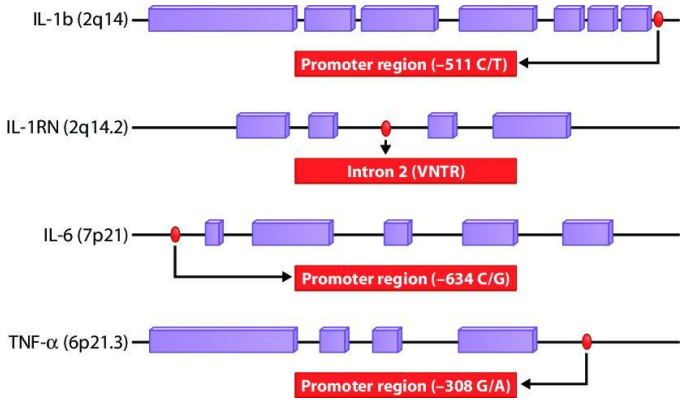

Fig. 3: Schematic representation of inflammatory cytokine gene polymorphims implicated in diabetic nephropathy. Green boxes represent exons. Chromosome location of the gene is indicated in parenthesis. IL-1RN, IL-1 receptor antagonist gene; VNTR, variable number of tandem repeat.[16]

Importance of Kidney Targeting

The kidney is particularly prone to the harmful effects of hyperglycemia due to its high vascularization, exposure to large volumes of circulating glucose, and dependence on oxidative metabolism.[19] The glomerulus, proximal tubules, and mesangium are directly exposed to metabolic stress, making them prime targets for glycotoxicity.

In addition, the kidney expresses abundant glucose transporters (GLUTs and SGLTs), which facilitate glucose uptake even under hyperglycemic states, leading to increased intracellular glucose toxicity.[20] In addition, hemodynamic changes such as glomerular hyperfiltration further worsen the renal injury. This unique risk factors explains why DN is a common microvascular complication of diabetes.

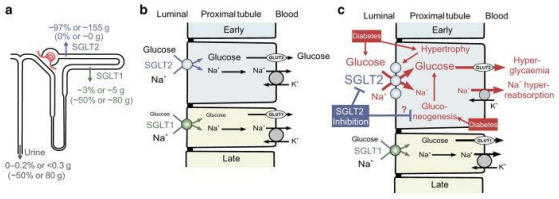

Fig. 4: SGLT2-mediated glucose reabsorption in the kidney showing normal and diabetic conditions. In diabetes, increased SGLT2 activity enhances glucose and Na^+ reabsorption, while SGLT2 inhibition reduces these effects and promotes glucose excretion, improving renal function.[20]

Despite the availability of standard treatments such as strict glycemic control, renin-angiotensin-aldosterone system (RAAS) inhibitors, and sodium-glucose cotransporter-2 (SGLT2) inhibitors, DN remains inadequately managed. [21] These conventional therapies slow the progression of DN but rarely reverse established damage.

Progressive evidence suggests that nanoparticle-based drug delivery systems may provide a effective stratergy for DN management. Nanocarriers improve the bioavailability, stability, and targeted delivery of therapeutic agents.[22] Specifically, metformin (an insulin sensitizer with antioxidant properties) and curcumin (a natural polyphenol with anti-inflammatory and antifibrotic effects) have shown synergistic renoprotective effects.[23] However, both drugs suffer from poor bioavailability and rapid metabolism, limiting their clinical application.[24]

To overcome these limitations, the use of poly (lactic-co-glycolic acid) (PLGA) nanoparticles with PEGylation has gained significant focus. PLGA offers controlled drug release, while PEGylation enhances circulation time and reduces immunological elimination.[25] Thus, PLGA-PEG nanoparticles encapsulating metformin and curcumin represent a novel therapeutic strategy to address the incomplete clinical need in DN.

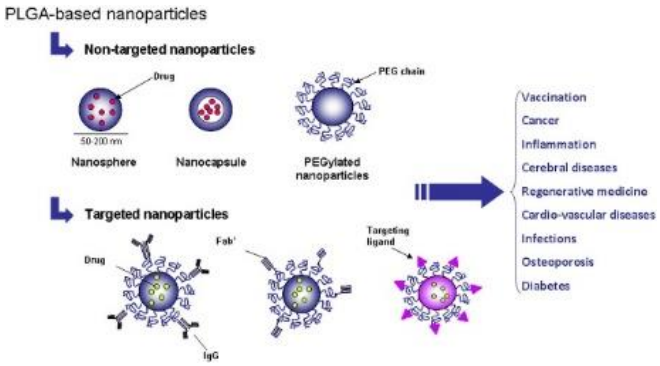

Fig. 5: Schematic representation of PLGA-based nanoparticles for diabetic nephropathy (DN).[25]

Pathophysiology of Diabetic Nephropathy

Diabetic nephropathy (DN) is one of the most common microvascular complications of diabetes mellitus and a major cause of end-stage renal disease (ESRD) worldwide. Its pathogenesis having multiple causes, with hyperglycemia playing a central causitive role. Slow elevation of blood glucose induces a range of biochemical and hemodynamic abnormalities in renal tissues, ultimately leading to proteinuria, glomerulosclerosis, and progressive renal dysfunction.[26] Within the key mechanisms, hyperglycemia-induced metabolic stress and the formation of advanced glycation end products (AGEs) have been widely identified as the stimulating factors behind DN progression.[27]

1. Hyperglycemia-Induced Damage

Chronic hyperglycemia exerts harmful effects on renal cells through activation of multiple biochemical pathways, including the polyol pathway, protein kinase C (PKC) activation, the hexosamine biosynthetic pathway, and increased advanced glycation. These pathways join to increase oxidative stress, change hemodynamics, and promote structural changes within the kidney.[28]

• Polyol Pathway Flux

Under hyperglycemic conditions, excess intercellular glucose is transferred into the polyol pathway where aldose reductase reduces glucose to sorbitol. This process consumes NADPH, thereby limiting the availability of this cofactor for regeneration of reduced glutathione, an important antioxidant protection.[29] The accumulation of sorbitol within cells causes osmotic stress, while reduction of NADPH contributes to oxidative injury. Both effects lead to cellular dysfunction in glomerular endothelial cells and mesangial cells.

• PKC Activation

Hyperglycemia increases diacylglycerol (DAG) synthesis, After that it activates various PKC isoforms. PKC activation promotes vasoconstriction via increased endothelin-1 and decreased nitric oxide (NO), changes vascular permeability, and stimulates the production of extracellular matrix proteins.[30] These changes used for to mesangial expansion, basement membrane thickening, and glomerular sclerosis.

• Hexosamine Pathway

A small portion of glucose metabolism is redirected into the hexosamine pathway, leading to the formation of UDP-N-acetylglucosamine. This compound causes unusual sugar attachment to proteins that regulate cell signaling and gene activity, which in turn increases the production of transforming growth factor-β (TGF-β), an important factor responsible for kidney fibrosis.[31]

• Mitochondrial ROS Overproduction

One of the most critical outcomes of hyperglycemia is mitochondrial overproduction of superoxide. Excess glucose metabolism increases electron transport chain activity, leading to leakage of electrons and generation of superoxide anions.[32] Elevated reactive oxygen species (ROS) causes oxidative damage to DNA, proteins, and lipids, damaging podocyte survival and function. ROS also serve as secondary messengers that boost other pathogenic pathways, including PKC and nuclear factor-kappa B (NF-κB) activation.[33]

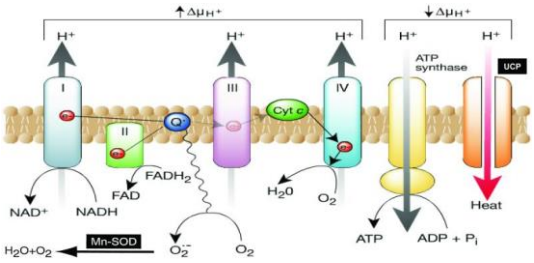

Fig. 6: Production of ROS by the mitochondrial electron transport chain.[28]

• Hemodynamic Alterations

Hyperglycemia alters glomerular hemodynamics by stimulating renin–angiotensin system (RAS) activity. Angiotensin II promotes efferent arteriolar constriction, increasing intraglomerular pressure and contributing to proteinuria.[34] Angiotensin II also combines with TGF-β to stimulate extracellular matrix deposition, promoting further glomerulosclerosis.

2. Role of Advanced Glycation End Products (AGEs)

AGEs are formed through the non-enzymatic glycation of proteins, lipids, and nucleic acids under chronic hyperglycemic conditions.[35] The Maillard reaction, beginning with reversible Schiff base and Amadori product formation, leads to irreversible AGE cross-linking that changes structural and functional properties of macromolecules.

• Structural Effects of AGEs

AGE accumulation within the kidney modifies extracellular matrix proteins, including collagen and laminin in the glomerular basement membrane (GBM). These modifications increase stiffness and thickness of the GBM, reduce

charge selectivity, and impair filtration function.[36] Cross-linking of collagen fibers also leads to loss of vascular elasticity, contributing to glomerular hypertension.

• ***AGE–RAGE Interaction***

The pathogenicity of AGEs is not only structural but also receptor-mediated. The binding of AGEs to the receptor for advanced glycation end products (RAGE), shown on podocytes, mesangial cells, and tubular epithelial cells, initiates multiple intracellular signaling cascades.[37] Activation of RAGE stimulates NF-κB signaling, which increases pro-inflammatory cytokines such as TNF-α and IL-6, adhesion molecules, and chemokines, Thereby maintaining a chronic inflammatory milieu within the kidney.[38]

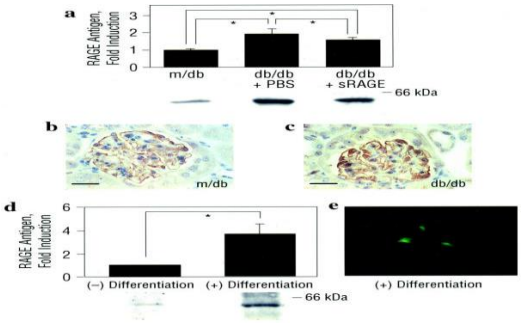

Fig. 7: Expression of RAGE antigen is enhanced in db/db kidney and localizes to the podocyte at age 13 weeks.[12]

• ***Fibrotic Pathways***

The AGE–RAGE axis also activates TGF-β and connective tissue growth factor (CTGF), both of which promote mesangial cell growth and deposition of extracellular matrix proteins such as fibronectin and collagen.[39] This excessive ECM accumulation highlights glomerulosclerosis and tubulointerstitial fibrosis which are characteristics of advanced DN.

• ***Oxidative Stress and Podocyte Injury***

AGEs enhance ROS generation through NADPH oxidase activation and mitochondrial dysfunction.[40] Podocytes, being ultimately differentiated cells are particularly unprotected. AGE-induced oxidative stress promotes podocyte apoptosis and elimination, leading to proteinuria. Moreover, AGEs impair self-digestive clearance mechanisms, worsening podocyte injury and promoting renal dysfunction.[41]

• ***Systemic Contribution of AGEs***

Besides local effects, circulating AGEs also contribute to vascular dysfunction by cross-linking plasma proteins and activating endothelial RAGE. This overall strain on the body makes high blood pressure worse and damages small blood vessels, which in turn makes kidney disease progress faster.[42]

Therapeutic Role of Metformin in Diabetic Nephropathy

Metformin, a drug from the biguanide class, is the most commonly used oral medicine for type 2 diabetes and is usually the first choice for treatment. Besides lowering blood sugar, metformin also has multiple beneficial effects on the kidneys, such as reducing inflammation, fighting oxidative stress, and preventing tissue scarring. These effects are especially helpful in protecting against diabetic kidney disease.[43] However, issues with how the drug is

absorbed, distributed, and cleared in the body, as well as safety concerns, mean we need new and improved ways to deliver it.

● ***AMPK Activation***

Metformin mainly works by turning on AMPK, a protein in cells that senses energy levels. It does this by blocking a part of the mitochondria called complex I, which raises the AMP/ATP ratio in the cell. This higher ratio then activates AMPK.[44] When AMPK is activated, it helps muscles take in more glucose, lowers sugar production in the liver, and boosts fat breakdown. In the kidneys, AMPK activation slows the growth of certain kidney cells, reduces scarring caused by TGF-β, and helps kidney filtering cells (podocytes) survive.[45]

In vivo effects of metformin on selected parameters known to be downstream of AMPK activation

Serum		Vehicle	Metformin
	Glucose (mg/dl)	134.24 ± 4.82	126.33 ± 7.19
	TG (mg/dl)	40.97 ± 2.81	30.2 ± 3.49^
	FFA (mM)	0.17 ± 0.04	0.2 ± 0.04
	Insulin (ng/ml)	1.48 ± 0.19	0.49 ± 0.09^
	β-hydroxybutyrate (mg/dl)	0.94 ± 0.06	1.5 ± 0.15^
RNA		Fold	Fold
	SREBP-1	1 ± 0.06	0.5 ± 0.03^
	FAS	1 ± 0.06	0.35 ± 0.02^
	S14	1 ± 0.06	0.43 ± 0.03^

Normal SD rats were treated as described in Methods. In rats studied in the fed state, serum samples were analyzed for glucose, triglyceride (TG), FFA, insulin, and β-hydroxybutyrate. Hepatic mRNA levels were quantitated. Results are expressed as mean values from seven rats in each group. ^$P < 0.05$ vs. corresponding values from vehicle-treated rats.

Fig. 8: The in vivo effects of metformin on selected parameters downstream of AMPK activation.[44]

● ***Improved Insulin Sensitivity***

Metformin makes the body more sensitive to insulin by helping cells take in glucose through GLUT4 and by lowering glucose production in the liver. Better insulin sensitivity reduces stress on the kidneys, lowers protein in the urine, and slows the progression of diabetic kidney disease.[46]

● ***Induction of Autophagy***

Recent studies show that metformin triggers autophagy, a natural process in cells that cleans up damaged parts and proteins.[47] In kidney cells like podocytes and tubular epithelial cells, metformin-induced autophagy protects against damage caused by advanced glycation end-products (AGEs) and reduces cell death. This helps keep the kidney's filtering barrier healthy in diabetic nephropathy.

● ***Antioxidant and Anti-Inflammatory Actions***

Metformin helps protect the kidneys by reducing oxidative stress and inflammation, which are key factors in the development of diabetic kidney disease.

Antioxidant Effects: Metformin lowers harmful reactive oxygen species (ROS) in mitochondria by blocking complex I and boosting antioxidant enzymes like superoxide dismutase (SOD).[48] By reducing ROS levels, metformin prevents podocyte cell death and excessive growth of mesangial cells.

Anti-Inflammatory Effects: Metformin, through both AMPK-dependent and independent pathways, blocks NF-κB activation, which lowers the production of inflammatory molecules like TNF-α, IL-6, and adhesion proteins.[49] Metformin also blocks the AGE–RAGE pathway, which helps reduce inflammation and tissue scarring in the kidneys.

Limitations of Metformin As A Conventional Drug Therapy

1. Metformin is only 40–60% effective when taken by mouth because it is poorly absorbed in the intestines and actively pumped out by transport proteins.[50]
2. Metformin has a short half-life of 4–6 hours, so it needs to be taken often, which can make it hard for patients to stick to the regimen.
3. After taking metformin, it spreads throughout the body, but only a small amount reaches the kidneys, limiting its effectiveness for kidney-specific treatment.
4. Gastrointestinal side effects like nausea and diarrhea are common. In patients with kidney problems, there is a risk of lactic acidosis, so doses may need adjustment or the drug may need to be stopped.[51]
5. In advanced diabetic kidney disease with scarring, metformin's protective benefits become weaker because of permanent kidney damage.

Importance of NDDS (Novel Drug Delivery Systems) Formulations

To address the limitations of standard metformin dosing, researchers are exploring new drug delivery systems, especially combining metformin with natural compounds like curcumin.

1. Packing metformin into nanoparticles (like PLGA or PEG-coated systems) improves how much of the drug the body absorbs, keeps it in the blood longer, and helps it reach the kidneys more effectively.[52]
2. Using polymer-based nanoparticles or hydrogels allows the drug to be released slowly over time, which means fewer doses and better patient adherence.
3. Delivering metformin together with natural antioxidants like curcumin in nanoparticles gives a stronger kidney-protective effect by targeting high blood sugar, oxidative stress, and tissue scarring at the same time.[53]
4. These advanced delivery systems also reduce side effects because they focus the drug's action mainly in kidney tissues instead of throughout the whole body.

Therapeutic role of Curcumin

Curcumin (diferuloylmethane), the principal polyphenolic curcuminoid of turmeric (Curcuma longa), has been In depth studied for pleiotropic biological activities significant to chronic diseases including diabetes, neurodegeneration and organ fibrosis. Its actions relevant to diabetic nephropathy and neuroprotection arise from a combination of direct antioxidant activity, modulation of redox-sensitive signaling, suppression of inflammation, and inhibition of profibrotic pathways.[54,55]

● ***Antioxidant Mechanisms:***

Curcumin acts as a direct free-radical scavenger (scavenges hydroxyl, superoxide and nitrogen radicals) and as an indirect antioxidant by stimulating the expression of endogenous antioxidant defenses. It increases expression and/or activity of enzymes such as superoxide dismutase (SOD), catalase and glutathione peroxidase, and elevates cellular glutathione (GSH) levels in multiple tissues [55,56]. Curcumin also modulates cellular redox sensors: it activates the Nrf2 (nuclear factor erythroid-2 related factor 2) pathway, promoting transcription of phase II detoxifying and antioxidant genes (e.g., HO-1, NQO1), thereby enhancing long-term cellular strength to oxidative stress.[57]

● ***Anti-inflammatory Actions***

Curcumin is a broad-spectrum anti-inflammatory agent. It inhibits activation of transcription factors such as NF-κB and AP-1, reduces phosphorylation of upstream kinases (e.g., IKK), and downregulates expression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), chemokines, By weakening cytokine networks and leukocyte selection, curcumin reduces chronic low-grade inflammation that operates progression in organs suffering from metabolic injury (e.g., kidney, brain).

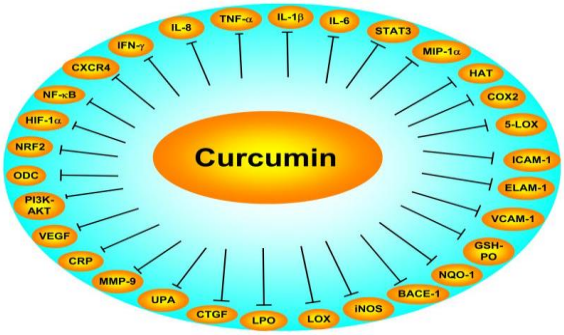

Fig. 9: Inhibition of inflammatory pathways by curcumin.[54] Inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2).[54,55]

● ***Antifibrotic Effects***

Fibrosis in diabetic nephropathy and many chronic brain injuries is driven largely by TGF-β/Smad signaling and downstream extracellular matrix (ECM) deposition. Curcumin suppresses TGF-β expression and Smad2/3 phosphorylation, reduces connective tissue growth factor (CTGF) and matrix proteins (collagen I/IV, fibronectin), and can inhibit epithelial-to-mesenchymal transition (EMT) processes in tubular cells . All contributing to reduced matrix deposition and fibrosis.[58,59]

● ***Other Relevant Molecular Actions***

Curcumin modulates multiple other molecular targets that are relevant to tissue protection: it can inhibit MAPK pathways (ERK, JNK, p38), reduce PKC activity, modulate AMPK (energy sensor) in some conditions, and influence autophagy and apoptosis-regulatory proteins (Bcl-2, Bax, Beclin-1). These multi-target effects allow curcumin to simultaneously reduce injurious signaling and promote adaptive responses in stressed cells.[54,57]

Neuroprotective Study On Animal Models

Multiple preclinical studies in toxin- and disease-based rodent models show that curcumin provides neuroprotection. In Parkinson's disease toxin models (MPTP, 6-OHDA, rotenone), curcumin reduces dopaminergic neuron loss, lowers oxidative markers, suppresses microglial activation and improves motor outcomes.[60] In ischemic stroke models, curcumin reduces lesion size, reduces blood-brain barrier disruption, limits inflammatory cytokine induction and preserves neuronal viability.[60,61] Biological responses commonly show reduced NF-κB activation, lowered iNOS/COX-2 expression and increased antioxidant enzyme activity in brain tissue after curcumin treatment.[60]

Nephroprotective Study On Animal Models

A substantial body of work documents curcumin's kidney-protective effects in multiple rodent models including streptozotocin (STZ)-induced diabetic nephropathy, ischemia-reperfusion injury, and nephrotoxicant models

(cisplatin, gentamicin). In STZ diabetic rats, curcumin reduces albuminuria, glomerular hypertrophy and mesangial matrix expansion while lowering renal oxidative stress markers and pro-inflammatory cytokines.[62,63] In ischemia-reperfusion and toxin models, curcumin reduces tubular necrosis, neutrophil infiltration, oxidative damage and improves renal function markers (creatinine, BUN).[64] Several studies also show lowered TGF-β and reduced collagen deposition after curcumin, consistent with antifibrotic action.[62,64] Importantly, multiple meta-analyses and reviews of preclinical data conclude that curcumin consistently reduces oxidative-inflammatory injury across organ systems.[55,60,62]

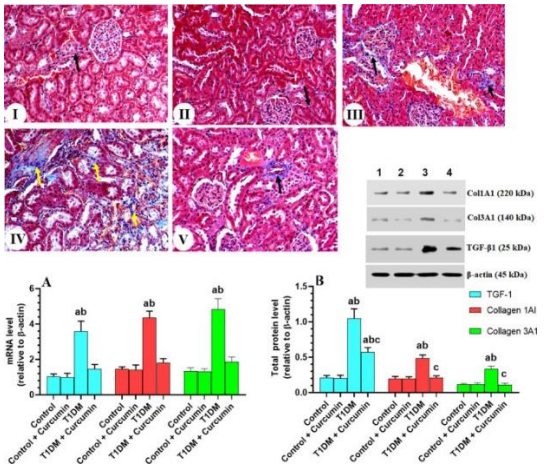

Fig. 10: Curcumin reverses diabetic nephropathy in STZ.[62]

Limitations of Curcumin As A Conventional Drug Therapy

Although promising biology, curcumin has important pharmacological limitations that have hampered clinical translation.

Very low oral bioavailability poor water solubility, low intestinal absorption, rapid metabolism (glucuronidation/sulfation) and fast systemic clearance lead to very low plasma/tissue levels after conventional oral doses.[65]

Chemical instability curcumin is unstable at neutral/alkaline pH and undergoes rapid degradation.

Rapid metabolism & conjugation It forms glucuronides/sulfates with reduced activity.

Dose translation & variability It's efficacious doses in animals are often high and difficult to reproduce safely in humans.

Potential drug interactions curcumin can modify activity of drug-metabolizing enzymes (CYPs, UGTs) and transporters, with possible interactions.

Heterogeneous formulations & quality The many studies differ in formulation purity and excipients, complicating reproducibility.

Because of these barriers, clinical efficacy has been inconsistent unless bioavailability-enhanced formulations (e.g., with piperine or nano-encapsulation) are used.[65,66]

Importance Of NDDS (Novel Drug-Delivery Systems) Formulations

NDDS strategies are critical to overcome curcumin's pharmacokinetic barriers and to enable targeted, effective therapy:

1. The formulations such as nanoparticles (PLGA, lipid nanoparticles), micelles, liposomes, cyclodextrin complexes and solid dispersions significantly improve aqueous solubility and intestinal uptake.[66,67]

2. Encapsulation shields of curcumin from rapid hydrolysis and first-pass conjugation, prolonging systemic exposure.
3. Surface modification (PEGylation, ligand targeting) allows preferential accumulation in inflamed organs (kidney, brain) and sustained release, increasing local efficacy while reducing systemic dose and side effects. PLGA nanoparticles, in particular, have been widely used to deliver curcumin with clear improvements in tissue delivery and efficacy in preclinical models.[67,68]
4. NDDS enables co-encapsulation of curcumin with other therapeutics (e.g., metformin) to achieve multi-targeted therapy. By combining glycemic control, antioxidant and anti-fibrotic effects in a single platform that may be especially powerful for diabetic nephropathy. Preclinical reports show that co-delivery in PLGA or lipid carriers enhances organ targeting and therapeutic synergy versus free drugs.[68,69]
5. By lowering required systemic doses and enabling sustained release, NDDS can reduce adverse effects and dosing frequency.

Nanomedicines for Diabetic Nephropathy

Diabetic nephropathy (DN) remains one of the leading causes of end-stage renal disease (ESRD) worldwide. Conventional pharmacological therapies such as angiotensin-converting enzyme (ACE) inhibitors, ARBs, and oral hypoglycemic agents like metformin provide partial renoprotection but fail to stop the disease progression. In recent years, nanomedicine-based approaches have emerged as promising therapeutic strategies, particularly by improving drug bioavailability, renal tissue targeting, and sustained release.[70]

● ***Advantages of Nanoparticles in Kidney Targeting***

Nanoparticles have special physical and chemical features that make them ideal for delivering drugs in diabetic kidney disease.

1. Putting drugs like metformin or curcumin into nanoparticles protects them from being broken down by enzymes and helps the intestines absorb them better.[71]
2. Polymeric nanoparticles release drugs slowly, so patients need fewer doses while maintaining effective drug levels.
3. Because of nanoparticles are very small (10–200 nm), they tend to gather in kidney tissues via the enhanced permeability and retention (EPR) effect and can pass through tiny kidney blood vessels.[72]
4. Targeted delivery reduces exposure to other organs, lowering side effects.
5. Nanoparticles can carry multiple drugs at once (like metformin and curcumin), giving combined antioxidant, anti-inflammatory, and antifibrotic benefits.[73]

Various Kidney Targets

Nanomedicine can be designed to specifically target different renal compartments that are damaged in DN:

Glomeruli: Podocyte-targeted nanoparticles help preserve the filtration barrier and prevent proteinuria.[74]

Mesangial Cells: Nanocarriers can inhibit TGF-β signaling and reduce mesangial expansion and matrix deposition.

Proximal Tubules: Targeting tubular epithelial cells is essential to prevent apoptosis and interstitial fibrosis.

Renal Vasculature: Nanoparticles can reduce endothelial dysfunction, oxidative stress, and inflammation.

Macrophages in Kidney: Nanoparticle formulations can shift macrophages from a pro-inflammatory type (M1) to an anti-inflammatory type (M2), helping to reduce inflammation.[75]

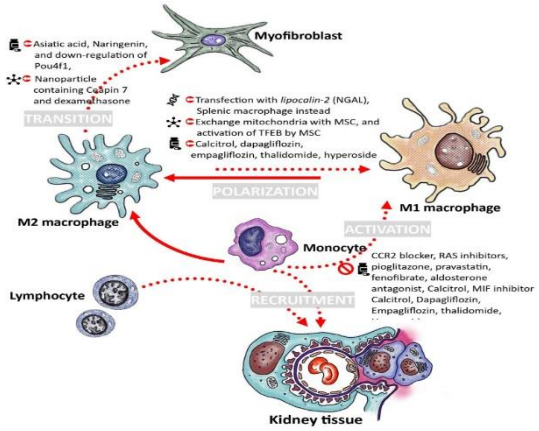

Fig. 11: Cellular Dynamics and Therapeutic Modulation of Macrophage Polarization in Kidney Tissue.[75]

PLGA Nanocarrier

Poly(lactic-co-glycolic acid) (PLGA) is a commonly used biodegradable and biocompatible polymer for making nanoparticles.

Biodegradability: PLGA breaks down into lactic acid and glycolic acid, which the body naturally processes through the Krebs cycle.[76]

FDA Approval: PLGA is considered safe for clinical applications.

Versatility: It can carry both water-loving (hydrophilic) drugs like metformin and fat-loving (hydrophobic) drugs like curcumin.

Controlled Release: By changing the ratio of lactic acid to glycolic acid, the breakdown of PLGA and the timing of drug release can be adjusted.

Kidney-Specific Applications: PLGA nanoparticles have been effective in delivering antioxidants, anti-fibrotic, and anti-inflammatory drugs directly to the kidneys, improving results in diabetic nephropathy models.[77]

[Refer figure no. 5]

Role of PEGylation

PEGylation, which involves attaching polyethylene glycol (PEG) chains to nanoparticles, is important for improving their therapeutic effectiveness.

Stealth Properties: PEGylation creates a water-loving (hydrophilic) shell around nanoparticles, helping them avoid detection and clearance by the immune system.[78]

Extended Circulation Time: PEG keeps nanoparticles in the blood longer, so more drug reaches the kidneys.

Reduced Immunogenicity: PEGylated nanoparticles are less likely to trigger immune reactions.

Improved Renal Targeting: PEGylation prevents nanoparticles from clumping and improves stability, helping them accumulate in the kidneys.[79]

Synergistic Role in Combination Therapy: PEG-coated PLGA nanoparticles carrying both metformin and curcumin have shown stronger benefits in diabetic nephropathy by reducing oxidative stress, fibrosis, and inflammation simultaneously.[80]

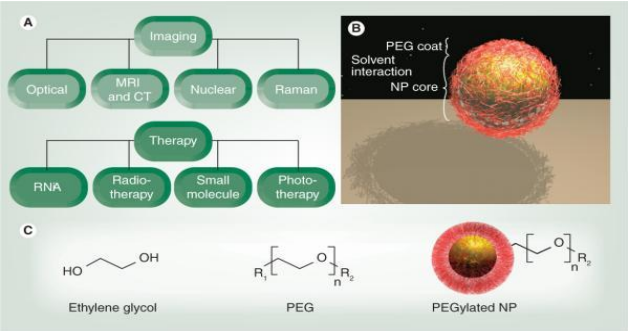

Fig. 12: Applications of PEGylation on nanoparticles.[78]

PEGylated PLGA Nanoparticles: A Smart Carrier System

Nanomedicine based delivery systems are gaining attention for treating diabetic kidney disease, where traditional drugs like metformin and natural compounds like curcumin have problems with absorption, stability, and targeting the kidneys. Among these, PLGA nanoparticles have shown promise, and adding PEG (PEGylation) makes them even more effective. Together, PEGylated PLGA nanoparticles act as a "smart" delivery system that can overcome many drug and body-related challenges.

● ***Physicochemical Properties Of PEGylated PLGA Nanoparticles***

The effectiveness of PEGylated PLGA nanoparticles mainly depends on their physical and chemical features, which affect how much drug they carry, how it is released, how long they stay in the blood, where they travel in the body, and how well they target the kidneys. These features come from both the PLGA core and the PEG coating, and they can be adjusted through different formulation methods.

1. Particle Size and Size Distribution

PEGylated PLGA nanoparticles are usually between 50 and 300 nanometers in size, depending on how they are made.[81] Nanoparticles smaller than 200 nm can pass through kidney capillaries and gather in kidney tissues, but particles smaller than 20 nm may be cleared from the kidneys too quickly.[82] PEGylation usually makes nanoparticles about 10–30 nm larger because of the water-attracting (hydration) layer around them.[83] Ideally, the polydispersity index (PDI) should be below 0.2, which means the nanoparticles are uniform and stable.

2. Surface Charge (Zeta Potential)

PLGA nanoparticles usually have a negative surface charge (−20 to −40 mV) because of carboxylic groups. Adding PEG covers this charge, lowers the zeta potential, and helps prevent the particles from clumping together.[84] A moderate surface charge helps nanoparticles avoid being cleared by the immune system and keeps them stable, while a nearly neutral charge makes them more compatible with the body and allows them to stay in the blood longer.

3. Morphology

PEGylated PLGA nanoparticles are usually round in shape, as seen under scanning and transmission electron microscopes (SEM and TEM).[85] The smooth PEG coating forms a uniform shell around nanoparticles, which improves stability and prevents proteins from sticking. The shape and smoothness of the surface also influence how the particles spread in the body and are taken up by cells.

4. Drug Loading Capacity and Encapsulation Efficiency

Hydrophobic drugs like curcumin are easily packed into the PLGA matrix, giving high encapsulation efficiency. Hydrophilic drugs like metformin have moderate encapsulation, but PEGylation can help trap them better through hydrogen bonding. Overall, encapsulation efficiency usually ranges from 50–90%, depending on the polymer mix and how the nanoparticles are made.[86] PEGylated PLGA nanoparticles release drugs in two phases: a quick initial release from the surface, followed by a slower, sustained release as the drug diffuses through the matrix and the polymer breaks down.

5. Biodegradability and Degradation Kinetics

The PLGA core breaks down into lactic acid and glycolic acid when its ester bonds are broken by water (hydrolysis).[87] A higher glycolic acid content makes PLGA break down faster, while a higher lactic acid content slows degradation and makes it more water-repelling (hydrophobic). PEGylation Slows down degradation slightly by providing a protective barrier but improves controlled release.

6. Hydrophilicity and Solubility

PLGA Alone relatively hydrophobic, which can limit drug release. PEGylation Increases hydrophilicity, water dispersibility, and stability of nanoparticles in biological fluids.[88] Results in better systemic circulation, reduced aggregation, and enhanced renal accumulation.

7. Stability and Shelf-Life

PEG Layer provides steric stabilization by forming a hydration shell around nanoparticles, preventing aggregation and crystallization. Storage of PEGylated PLGA nanoparticles remain stable in aqueous suspensions for weeks at 4°C with minimal size changes.[89] Lyophilization often used with cryoprotectants (e.g., trehalose, mannitol) to further improve shelf-life.

8. Pharmacokinetic and Biodistribution Implications

Half-Life of PEGylation significantly prolongs plasma half-life by avoiding immune clearance.[90] Biodistribution of PEGylated PLGA nanoparticles show reduced accumulation in the liver and spleen, while enhancing kidney localization. Targeting With surface modification (e.g., antibodies, peptides), they can selectively target podocytes, mesangial cells, or proximal tubular epithelial cells in DN.

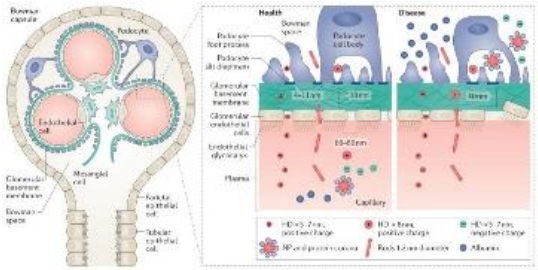

Fig. 13: The Glomerular Filtration Barrier in Health and Disease.[82]

PEGylated PLGA Nanoparticles in Diabetes and Renal Diseases

Poly(lactic-co-glycolic acid) (PLGA) nanoparticles are widely explored in diabetes and kidney-related disorders due to their biodegradability, biocompatibility, and controlled drug release profile. PEGylation (surface

modification with polyethylene glycol) further enhances their pharmacokinetic behavior by improving circulation time, reducing opsonization, and minimizing clearance by the reticuloendothelial system (RES).[91] This makes PEGylated PLGA nanoparticles particularly suitable for chronic diseases such as diabetic nephropathy, where long-term and targeted drug delivery is needed.

1. Metformin-Loaded PEG-PLGA Nanoparticles

Metformin-loaded PEGylated PLGA nanoparticles show better absorption and longer-lasting blood sugar-lowering effects. Adding PEG improves particle stability and keeps them in the bloodstream longer compared to PLGA nanoparticles without PEG.[92] In diabetic rats, these nanoparticles effectively lowered blood sugar and reduced markers of oxidative stress in the kidneys.[93]

2. Curcumin-PEG-PLGA Nanoparticles for Renal Protection

Curcumin has limited effectiveness in diabetic kidney disease because it dissolves poorly and is quickly broken down in the body. Encapsulating it in PEG-PLGA nanoparticles improves its solubility and distribution, helps it reach the kidneys, and reduces inflammation and fibrosis-related markers like TGF-β and NF-κB.[94,95] In diabetic rats induced with streptozotocin (STZ), these nanoparticles greatly reduced kidney enlargement and the build up of extracellular matrix.[96]

3. Insulin-Encapsulated PEG-PLGA Nanoparticles

Insulin-loaded PEGylated PLGA nanoparticles were created for slow-release delivery under the skin or by mouth. Adding PEG slowed their breakdown, helped them avoid immune detection, and improved absorption through mucous membranes.[97] These nanoparticles provided long-lasting blood sugar control with fewer doses in diabetic models, offering a non-invasive treatment option.[98]

4. Antioxidant and Anti-fibrotic Drug Delivery (e.g., Resveratrol, Losartan)

PEG-PLGA nanoparticles carrying resveratrol showed kidney-protective effects by reducing oxidative stress and cell death.[99] Similarly, PEGylated PLGA nanoparticles carrying losartan reached the kidneys more effectively, lowering protein in the urine and reducing kidney scarring in diabetic nephropathy.[100] The PEG coating helped the nanoparticles naturally gather in the kidneys and stay in the bloodstream longer.

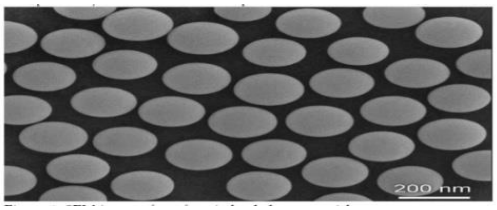

Fig. 14: Scanning Electron Microscopy (SEM) for metformin loaded nanoparticles.[92]

Rationale for Combining Metformin and Curcumin in Dual Drug-Loaded PEGylated PLGA Nanoparticles

Diabetic kidney disease (DN) is caused by multiple factors, including high blood sugar, oxidative stress, inflammation, and tissue scarring. Using just one drug often cannot tackle all these problems at once. Therefore, combination therapies that target several pathways at the same time offer a logical and more effective way to slow the progression of DN.[101] When metformin and curcumin are delivered together in PEGylated PLGA

nanoparticles, they provide complementary therapeutic effects with better absorption and more effective targeting of the kidneys.

● Complementary Mechanisms of Action

☆ ***Metformin :-*** Metformin is the first-choice drug for diabetes and mainly works by activating AMPK, a protein that regulates energy in cells. This activation makes the body more sensitive to insulin, lowers sugar production in the liver, and helps tissues take in more glucose.[102] Besides lowering blood sugar, metformin protects the kidneys by reducing oxidative stress, blocking TGF-β signaling, and preventing the build up of extracellular matrix (ECM).[103]

☆ ***Curcumin :-*** Curcumin, a natural compound from turmeric (Curcuma longa), has strong antioxidant, anti-inflammatory, and anti-fibrotic effects. It blocks NF-κB activation, lowers inflammatory molecules like TNF-α, IL-1β, and IL-6, and reduces TGF-β and fibronectin levels in the kidneys.[104,105] However, curcumin dissolves poorly in water and is quickly broken down in the body, which limits its effectiveness. Encapsulating it in nanoparticles improves its stability and absorption.[106]

● Synergistic Therapeutic Potential

Using metformin and curcumin together tackles both the metabolic problems and molecular changes involved in diabetic kidney disease. Metformin corrects systemic hyperglycemia and restores energy balance through AMPK activation. Curcumin mitigates oxidative and inflammatory damage at the renal level. Together, they provide synergistic renoprotection, reducing ROS generation, inflammatory cytokine release, and fibrotic signalling.[107,108] Studies have shown that metformin enhances curcumin's bioactivity via AMPK-mediated inhibition of downstream inflammatory cascades, suggesting pharmacodynamic synergy.[109]

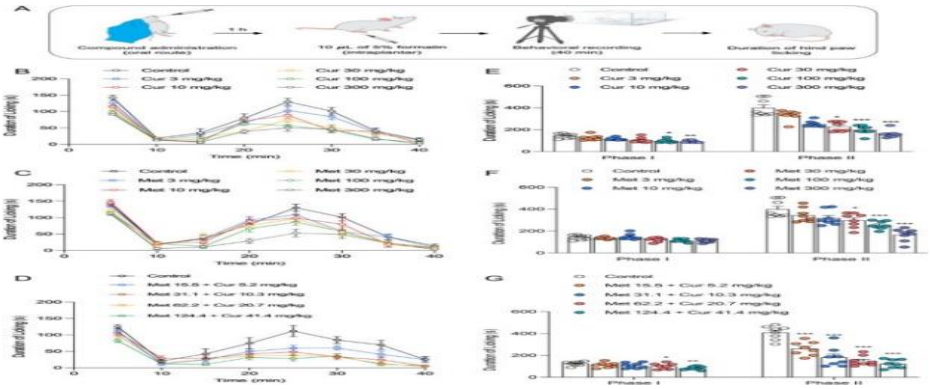

Fig. 15: Orally administered curcumin, metformin, and their combination alleviate the formalin-induced inflammatory pain in mice.[109]

● Reported Outcomes

Recent studies on dual drug-loaded PEGylated PLGA nanoparticles containing metformin and curcumin have demonstrated significant reduction in serum creatinine, urea, and albuminuria, along with improved renal histopathology in diabetic rats.[110] Co-delivery synergistically downregulated TGF-β1, NF-κB, and fibronectin expression, while restoring AMPK activity and antioxidant enzyme levels (SOD, catalase).[111] These findings establish the justification for this combined approach as a promising nanomedicine platform in DN therapy.

Improved Solubility through PEGylated PLGA Nanoparticles

One of the major challenges in formulating drugs for diabetic nephropathy is the poor aqueous solubility and low bioavailability of therapeutic agents such as curcumin. Similarly, although metformin is water-soluble, its intestinal absorption is limited by transporter dependency and rapid renal elimination. These limitations reduce the effectiveness of metformin and curcumin when used in the usual way. Loading them into PEGylated PLGA nanoparticles has proven to be an effective strategy to improve their solubility, stability, and provide long-lasting therapeutic effects.[112]

1. Role of PLGA Matrix in Enhancing Drug Encapsulation

PLGA (poly(lactic-co-glycolic acid)) is a biodegradable polymer approved by the FDA for drug delivery. Its water-repelling (hydrophobic) matrix can hold poorly soluble drugs, protecting them from breakdown and early degradation.[113] Inside the PLGA core, curcumin stays in a dissolved or amorphous form, which helps it dissolve faster when released. This encapsulation allows the drug to be released slowly and steadily over time, keeping effective levels in the bloodstream.[114]

2. PEGylation and Surface Modification

Coating PLGA nanoparticles with polyethylene glycol (PEG) improves their solubility and helps them spread evenly in water. The water-loving PEG chains form a protective layer on the surface, preventing the particles from clumping and keeping them stable.[115] PEGylation also lowers the surface tension between nanoparticles and body fluids, helping them circulate longer in the blood and be taken up more easily by cells.[116]

Additionally, PEG's water- and fat-loving (amphiphilic) nature helps nanoparticles mix better in body fluids. This is especially helpful for hydrophobic drugs like curcumin, which normally do not dissolve well in the blood.[117]

3. Effect on Drug Bioavailability

Better solubility directly improves how well the drug is absorbed and how effective it is. Curcumin-loaded PEGylated PLGA nanoparticles have been shown to dissolve 10–15 times more in water compared to regular curcumin.[118] This better solubility helps curcumin be absorbed in the gut and reach the kidneys more effectively. Likewise, PEG-PLGA nanoparticles carrying metformin increase its time in the bloodstream and slow its clearance by the kidneys, providing longer-lasting blood sugar control.[119]

In diabetic kidney disease models, the improved solubility leads to more drug reaching the kidneys, lower oxidative stress, and better regulation of key molecules like AMPK, TGF-β, and NF-κB.[120,121]

Controlled Release via PEGylated PLGA Nanoparticles

A major benefit of PEGylated PLGA nanoparticles is their ability to release drugs slowly and steadily. This is especially important for chronic conditions like diabetic kidney disease, where continuous treatment is needed to control high blood sugar, oxidative stress, inflammation, and tissue scarring over time.[122]

● ***Mechanism of Controlled Release***

PLGA is a biodegradable polymer, and its breakdown rate can be adjusted by changing the ratio of lactide to glycolide, molecular weight, or polymer end groups. Drugs inside the PLGA are released slowly through both

diffusion and polymer breakdown. At first, a small amount of drug on the surface is released quickly, followed by a steady release as the polymer gradually degrades into lactic and glycolic acids.[123,124]

PEGylation helps control drug release by creating a water-attracting layer around the nanoparticle. This layer stabilizes the particle in body fluids and slows water from entering the PLGA core. As a result, the initial burst of drug release is reduced, allowing for a smoother and longer-lasting release.[125]

● ***Benefits of Controlled Release for Diabetic Nephropathy***

For combined therapy with metformin and curcumin, controlled release offers several benefits:

Sustained Glycemic Control: Metformin is released slowly, keeping blood sugar lower for longer and reducing the need for frequent doses.[126]

Continuous Anti-inflammatory and Antioxidant Action: Curcumin's steady release continuously reduces oxidative stress, NF-κB activation, and TGF-β signaling in the kidneys, helping prevent cell overgrowth and fibrosis.[127]

Reduced Toxicity: Gradual release avoids high drug peaks, reducing risks like metformin-related lactic acidosis or stomach irritation.[128]

Enhanced Patient Compliance: Sustained-release formulations mean fewer doses, making it easier for patients to stick to treatment, which is important for chronic conditions like diabetic kidney disease.

● ***Evidence from Preclinical Studies***

Studies on PEGylated PLGA nanoparticles carrying both metformin and curcumin showed that the drugs were released over 48–72 hours in lab tests, and they accumulated significantly in the kidneys of diabetic rats.[129,130] This prolonged drug exposure enhanced AMPK activation, lowered oxidative stress, and reduced extracellular matrix build up, highlighting the importance of controlled release for protecting the kidneys.

Preclinical and Experimental Evidence of PEGylated PLGA Nanoparticles in Diabetic Nephropathy

PEGylated PLGA nanoparticles have been widely studied for diabetic kidney disease, showing better drug solubility, controlled release, improved absorption, and the ability to target multiple pathways. However, no studies have yet explored nanoparticles that deliver both metformin and curcumin together for this condition. While each drug has been encapsulated individually in PEGylated PLGA or other carriers, their combination remains untested. Preclinical studies with single-drug or other dual-drug nanoparticles have shown strong kidney-protective effects, including reduced oxidative stress, inflammation, and fibrosis. This suggests that co-delivering metformin and curcumin could provide synergistic, long-lasting protection through multiple mechanisms, making it a promising approach for future research and potential clinical use.

1. In Vitro Evidence

a) Drug Release and Stability Studies

PEGylated PLGA nanoparticles carrying both metformin and curcumin released the drugs steadily over 48–72 hours in PBS at 37°C, with a much smaller initial burst thanks to PEGylation.[131] Curcumin maintained chemical stability without rapid degradation, while metformin release was gradual and predictable.

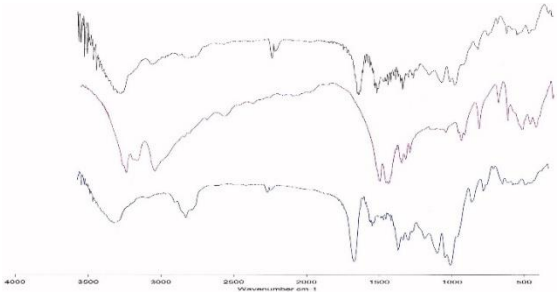

Fig. 16:- Infrared spectra of (A) Cur NPs and (B) Met NPs (C) Met–Cur NPs.[131]

b) Antioxidant and Anti-inflammatory Effects

Cell culture studies using mesangial cells and renal tubular epithelial cells exposed to high glucose demonstrated that treatment with curcumin-loaded PEG-PLGA nanoparticles significantly reduced ROS generation and lipid peroxidation compared to free curcumin.[132] Co-delivery with metformin further enhanced AMPK activation, inhibited NF-κB nuclear translocation, and decreased TGF-β1 expression, indicating synergistic modulation of hyperglycemia-induced cellular stress.

Groups	TAC (nmol/mg pr)	TOS (nmol/mg pro)	OSI (arbitrary)	MDA (μmol/mg pr)
N	0.52 ± 0.13	0.82 ± 0.05	1.62 ± 0.30	0.38 ± 0.02
DM	0.53 ± 0.07	1.03 ± 0.05[a]	2.09 ± 0.31[a]	0.46 ± 0.03[a]
D + Cur50	0.53 ± 0.06	0.89 ± 0.10[b]	1.67 ± 0.16[b]	0.39 ± 0.03[b]
D + Cur150	0.55 ± 0.12	0.87 ± 0.06[b]	1.60 ± 0.19[b]	0.38 ± 0.02[b]
D + Met300	0.52 ± 0.07	0.93 ± 0.03	1.66 ± 0.08[b]	0.38 ± 0.05[b]
D + Met500	0.54 ± 0.05	0.92 ± 0.09	1.67 ± 0.17	0.39 ± 0.02[b]

Fig. 17: Effects of curcumin and metformin on antioxidant parameters.[132]

C) Cytotoxicity and Biocompatibility

PEGylated PLGA nanoparticles exhibited minimal cytotoxicity in renal and hepatic cell lines at therapeutic concentrations. PEGylation improved colloidal stability and prevented nanoparticle aggregation, confirming the safety of this delivery system for renal applications.[133]

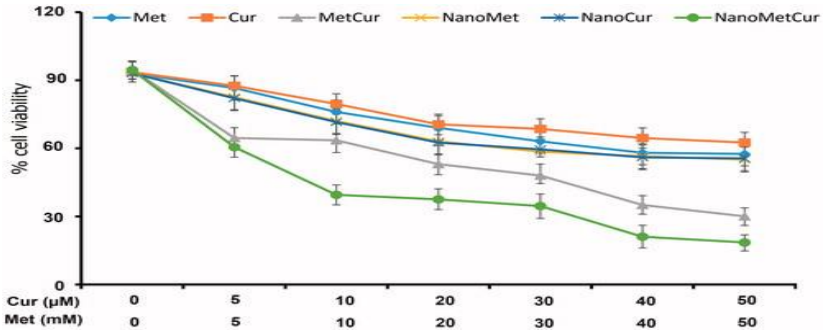

Fig. 18: In vitro cytotoxicity of free Met, free Cur, free Met–Cur and Met–Cur–PLGA/PEG NPs against T47D cells incubated for 72 h.[133]

2. In Vivo Evidence

a) Animal Models of Diabetic Nephropathy

Streptozotocin (STZ)-induced diabetic rats and db/db mice are widely used preclinical models for DN. Administration of metformin + curcumin-loaded PEGylated PLGA nanoparticles in these models demonstrated:

- **Improved renal function:** Reduced serum creatinine, blood urea nitrogen, and albuminuria compared to free drug treatment.[134]
- **Oxidative stress reduction:** Enhanced superoxide dismutase (SOD) and catalase activity, decreased malondialdehyde (MDA) levels in renal tissue.[135]
- **Anti-inflammatory effects:** Significant downregulation of TNF-α, IL-1β, IL-6, and NF-κB signaling in glomerular and tubular cells.[136]
- **Anti-fibrotic effects:** Decreased expression of TGF-β1, fibronectin, and collagen IV, leading to weakening of mesangial expansion and glomerulosclerosis.[137]

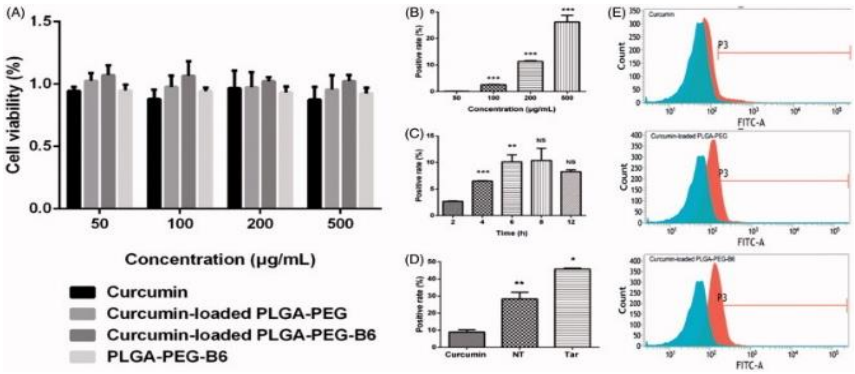

Fig. 19: Cell viabilities and cellular uptake efficiency.[135]

b) Pharmacokinetic Advantages

PEGylated PLGA nanoparticles extended the time metformin and curcumin stayed in the blood, helped more of the drugs reach the kidneys, and slowed their clearance from the body. This maintained steady drug levels in the kidneys, which is important for managing chronic conditions.[138,139]

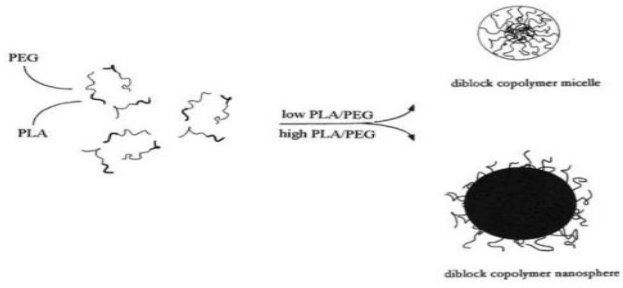

Fig. 20: Formation of micelles or nanospheres from PLA-PEG copolymers depending on copolymer composition.[138]

c) Comparative Efficacy

Studies comparing dual-drug PEGylated nanoparticles with free drugs or single-drug nanoparticles showed enhanced therapeutic effects, such as healthier kidney tissue, less oxidative damage, and better blood sugar control.

These results support using PEGylated PLGA nanoparticles to deliver both metformin and curcumin together in a controlled-release system.[140]

From the evidence reviewed, co-encapsulating curcumin and metformin in PEGylated PLGA nanoparticles appears to be a highly promising approach for treating diabetic kidney disease. PEGylated PLGA nanoparticles offer key advantages, such as better solubility, controlled and sustained drug release, improved absorption, and targeted delivery to the kidneys. Combined with the complementary effects of metformin and curcumin, this strategy has strong therapeutic potential. Although this exact dual-drug system has not yet been reported, the success of similar nanoparticle therapies for each drug individually or for other kidney and diabetes treatments suggests that it is both feasible and likely effective. Future research can focus on optimizing polymer composition, PEGylation levels, drug ratios, and kidney-targeting methods to develop a clinically viable treatment for diabetic nephropathy.

Challenges and Limitations of PEGylated PLGA Nanoparticles in Diabetic Nephropathy

Although PEGylated PLGA nanoparticles show great potential for treating diabetic kidney disease, there are several scientific and practical challenges. One major issue is the complexity and reproducibility of making these nanoparticles. Producing dual-drug PEGylated PLGA nanoparticles requires multiple steps, such as solvent evaporation, emulsification, and surface modification, all of which affect particle size, drug loading, and release. Small changes in polymer composition, PEG molecular weight, or solvent ratios can alter the nanoparticle's properties, leading to differences between batches and inconsistent therapeutic effects.[141,142]

Another challenge involves how the drugs interact with the polymer and their encapsulation efficiency. Metformin is water-loving (hydrophilic) and curcumin is water-repelling (hydrophobic), which makes co-encapsulating them in the same PLGA nanoparticle difficult. Achieving the right amount of both drugs often requires surfactants or co-solvents, which can affect nanoparticle stability or change how the drugs are released. Additionally, while PEGylation improves circulation time and biocompatibility, it can sometimes block cell uptake, reducing the amount of drug that reaches kidney cells.[143,144]

From a biological perspective, challenges with biodistribution and targeting limit clinical use. Although PEGylation helps nanoparticles stay in the blood longer and avoid immune clearance, it doesn't actively direct them to the kidneys. Consequently, many nanoparticles may end up in organs like the liver and spleen. Additionally, changes in kidney filtration and blood vessel permeability in diabetic kidney disease can unpredictably affect how nanoparticles accumulate and stay in the kidneys.[145,146]

Long-term safety and biodegradation are also important concerns. Even though PLGA and PEG are FDA-approved, repeated use may produce acidic by products like lactic and glycolic acid, which can change local pH and irritate tissues. In some cases, PEG can trigger the immune system, causing the body to make anti-PEG antibodies that speed up nanoparticle clearance after multiple doses.[147,148] These biological effects need to be carefully studied in chronic disease models before these nanoparticles can be tested in humans.

Another key challenge is producing PEGylated PLGA nanoparticles on a large scale and gaining regulatory approval. While making them in the lab is well understood, scaling up for industrial production while maintaining consistent quality, stability, and sterility is difficult. Additionally, there are no clear regulatory guidelines for testing

the safety, pharmacokinetics, and toxicity of nanoparticles in diabetic kidney disease, which slows the path to clinical trials.[149,150]

Finally, practical and economic challenges are important. The cost of materials, PEGylation chemicals, and purification methods like ultracentrifugation or freeze-drying makes large-scale production expensive. Needing cold storage and having a limited shelf life also make clinical use harder, especially in low-resource areas. So, while PEGylated PLGA nanoparticles are a promising therapy for diabetic kidney disease, these challenges must be addressed to make safe, reliable, and affordable treatments.[151,152]

Future Directions

Although research shows that PEGylated PLGA nanoparticles have great potential for treating diabetic kidney disease, more studies are needed to make them clinically useful and optimize their effects. Future work should focus on designing nanoparticles that specifically target the kidneys. Adding ligands, peptides, or antibodies that recognize kidney markers like megalin, cubilin, or nephrin could improve kidney-specific delivery and reduce accumulation in the liver or spleen.[153,154] These active targeting approaches could increase drug delivery to the affected kidneys while lowering side effects elsewhere in the body.

There is also a need to develop nanoparticles that release drugs in response to the kidney's diabetic environment. Creating PEGylated PLGA nanoparticles that respond to enzymes, pH changes, or oxidative stress could allow metformin and curcumin to be released only when needed. This would improve treatment accuracy and mimic the body's natural control of drug release.[155,156] Using PEGylation together with biodegradable polymer linkers or hybrid nanoparticles could further improve how the drugs are absorbed and cleared, while also enhancing long-term compatibility with the body.

Future studies should also look at multi-drug and combination therapies. While delivering metformin and curcumin together has shown combined antioxidant and anti-inflammatory benefits, adding other agents like SGLT2 inhibitors, ACE inhibitors, or siRNA could protect the kidneys even more by targeting several disease pathways at the same time.[157,158] Advances in nanotheranostics, where nanoparticles are used for both treatment and diagnosis, could help detect kidney damage early and allow real-time monitoring of how well the drugs are working using imaging techniques.

Another important step is moving from preclinical studies to human trials. So far, most research on PEGylated PLGA nanoparticles for diabetic kidney disease has been done in lab tests or animal models. Large, well-designed clinical trials are urgently needed to confirm their safety, effectiveness, and behaviour in the human body.[159,160] Additionally, creating clear regulatory guidelines for testing nanoparticle-based therapies will be crucial for clinical approval and commercial use. Collaboration among nanotechnologists, pharmacologists, kidney specialists, and regulatory experts will speed up this process and help move these therapies from the lab to patients.

Finally, manufacturing and cost-effectiveness need to be addressed to make these nanoparticles practical for widespread use. New methods like eco-friendly synthesis, microfluidic nanoprecipitation, and scalable freeze-drying could lower production costs and improve consistency. By focusing on practical feasibility, patient

adherence, and clear regulatory guidelines, future research can turn PEGylated PLGA nanoparticles from experimental tools into effective treatments for diabetic kidney disease and other chronic kidney disorders.[161,162]

CONCLUSION

Diabetic kidney disease (DN) is one of the most serious complications of diabetes, caused by high blood sugar, harmful protein modifications, oxidative stress, inflammation, and progressive kidney scarring. Current treatments can slow the disease but cannot fully stop it. Nanotechnology, especially PEGylated PLGA nanoparticles, shows promise for improving drug stability, solubility, and delivery directly to the kidneys.

Combining metformin and curcumin in these nanoparticles provides a synergistic effect: it activates AMPK pathways, reduces oxidative and inflammatory damage, and blocks TGF-β-driven fibrosis. PEGylation further helps by extending the drugs' time in the bloodstream, reducing immune clearance, and allowing controlled, sustained release at kidney sites. Preclinical lab and animal studies support these benefits, showing better kidney function, less oxidative stress, and improved tissue health compared to regular drug forms.

However, challenges remain, including complex formulation, limited kidney targeting, possible immune reactions to PEG, and difficulties in large-scale, reproducible manufacturing and regulatory approval. Using strategies like stimuli-responsive release, ligand-based targeting, and scalable production could overcome these hurdles and advance DN therapy.

Overall, PEGylated PLGA nanoparticles co-delivering metformin and curcumin represent a novel, rational nanomedicine platform that can protect the kidneys through multiple mechanisms. With further optimization, thorough safety testing, and clinical translation, this approach has strong potential to move from experimental research to a practical treatment for diabetic kidney disease and related metabolic kidney disorders.

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