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AN APPROACH AND OVERVIEW OF PHARMACOTHERAPY FOR RENAL CONDITIONS

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Abstract: Treatment and management of kidney disease are presently putting a significant strain on the world community. The renal glomerulus, which filters blood and metabolic waste into urine, makes the kidneys the most vital organs in the human urinary system. The glomerular filtration mechanism functions as a barrier to medicinal drugs based on charge and/or molecular size. For this reason, it is difficult to distribute drugs to the kidneys, which leads to treatment failure in a number of renal diseases. Therefore, many strategies to enhance medication delivery over the glomerulus filtration barrier are being researched. From disease prevention to diagnosis and treatment, nanotechnology in medicine has the potential to significantly affect human health. Renal treatment has shown promise for nanomaterials with a range of physicochemical features, such as size, charge, surface, and shape, as well as unique biological characteristics, such high cellular internalization, low cytotoxicity, and adjustable biodistribution and pharmacokinetics. Various kinds of nanosystems have been used to provide medications to the kidneys. This study focuses on the capabilities of nanomaterials, such as hydrogels and nanoparticles, in overcoming several obstacles to medication delivery to the kidneys. Kidney-targeted medication delivery systems' most popular distribution routes and tactics are also covered.

Key words: renal delivery, kidney disorders, targeted delivery, drug release, glomeruli, nanoparticles, hydrogel.

INTRODUCTION

The development of drugs has been combined to treat several related lesions associated with kidney diseases. The prevalence of chronic kidney disease (CKD) among elderly persons has increased throughout

the last 20 years. An estimated 31 million people in the US have chronic kidney disease (CKD), which causes millions of deaths globally [1, 2]. This highlights how important it is to develop new medications and delivery methods for pharmaceuticals to the kidneys, especially when therapies aimed at certain cell types are being researched. Previous studies used the characteristics of endogenous low-molecular weight proteins' accumulation in the kidneys to passively target them, including insulin, lysozymes, and immunoglobulin light chain [3]. Low-molecular-weight proteins can diffuse into medications to enhance renal bioaccumulation, but they also have a propensity to undergo filtration and deposit in tubular cells, which restricts the range of disorders for which they can be used [4].

The renal system in mammals is a vital system that performs several tasks. Kidney diseases are a global health problem that annually impact millions of individuals. These issues are often separated into two categories: chronic kidney disease (CKD) and acute kidney injury (AKI). Mammals' renal systems are essential organs that carry out a variety of functions. Millions of people worldwide are impacted by kidney illnesses each year [5]. These problems are often divided into two groups: acute kidney injury (AKI) [9,10,11] and chronic kidney disease (CKD) [6,7, 8]. Common kidney disorders include glomerulonephritis [14], tubulointerstitial fibrosis [12], diabetic nephropathy [13], and nephrotic syndrome [12]. [15].

KIDNEY anatomy and function

By regulating the chemical composition of blood, removing excess water, excreting waste products, and producing essential hormones that support blood pressure management, preserve healthy bones, and prevent anemia, the kidneys contribute to the maintenance of body homeostasis. The kidney is composed of three sections: the renal pelvis, which gathers and empties urine into the ureter, the medulla on the inside, and the cortex on the outside (Figure 1). The smallest functional unit in the renal system, the nephron, is responsible for blood filtration and subsequent reabsorption. Every nephron consists of a distal tubule that is joined to a collecting duct, a proximal tubule, a Henle loop, and a glomerulus encircled by a Bowman capsule. The collecting duct system and the site of all nephron drainage are located in the renal pelvis. The glomerulus is made up of a network of capillaries encircled by visceral epithelial cells called podocytes. The glomerulus endothelial cells and podocytes are separated by negatively charged glycoproteins (heparin sulphate proteoglycans) and extracellular matrix (ECM) proteins such as collagen IV and laminin, which create a basement membrane. In the glomerulus, charged chemicals that need to cross the negatively charged filtration barrier of the glomerulus are harder to filter than plasma content below 36 Å Stokes radius.The glomerulus filters 180 liters every day, which includes a range of uremic waste products and necessary substances like glucose and amino acids that are reabsorption by the tubular system. Furthermore, the renal tubules reabsorb approximately 99% of the water that passes through the glomerulus in order to reduce water loss. The proximal tubular epithelial cells accumulate uremic waste products that are not filtered in the glomerulus because of their size, charge limitations, or attachment to plasma albumins. [36]

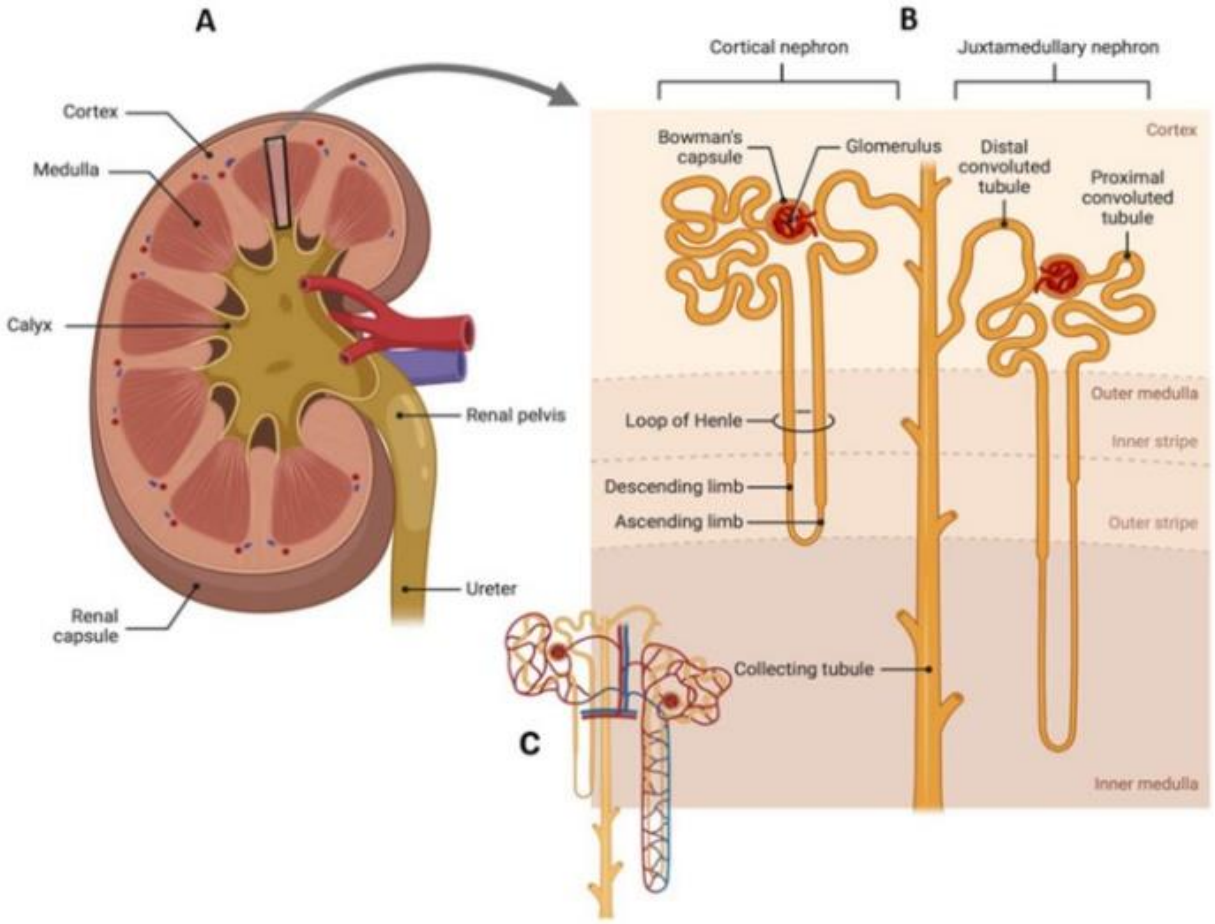

Figure 1: Schematic presentation of the renal system. (A) human kidney, (B) nephron, and (C) nephron with blood capillaries.

RENAL PATHOPHYSIOLOGY

The amount of cardiac output that goes to the kidneys is significantly higher than that of other vital organs including the liver, heart, and brain. Consequently, the glomerular pressure exposes the capillaries to vascular damage and the renal tissue is continuously vulnerable to potentially harmful compounds that are in circulation. Kidney damage is mostly caused by immune system disorders, ischemia, drug/xenobiotic toxicity, and genetics [37]. Nephron loss from renal injury puts more strain on the remaining functioning nephrons. By maintaining glomerular filtration rate (GFR) and intraglomerular pressure through the activation of the renin–angiotensin system and growth factors (transforming growth factor (TGF) and epidermal growth factor receptor (EGFR)), this high workload leads to glomerular hypertension and increases nephron size to compensate for the renal function. Podocyte hypertrophy, podocyte foot process separation, and glomerular basement membrane (GBM) rupture are the three main causes of protein leakage from glomeruli (Figure 2). Additionally, hyperfiltration raises the proximal convoluted tubules' (PCTs') rate of reabsorption, which might aggravate tubular injury by lysosomal destruction. Interstitial fibrosis and tubular atrophy may result from these inflammatory alterations in the tubules, which are encouraged by these processes [38].

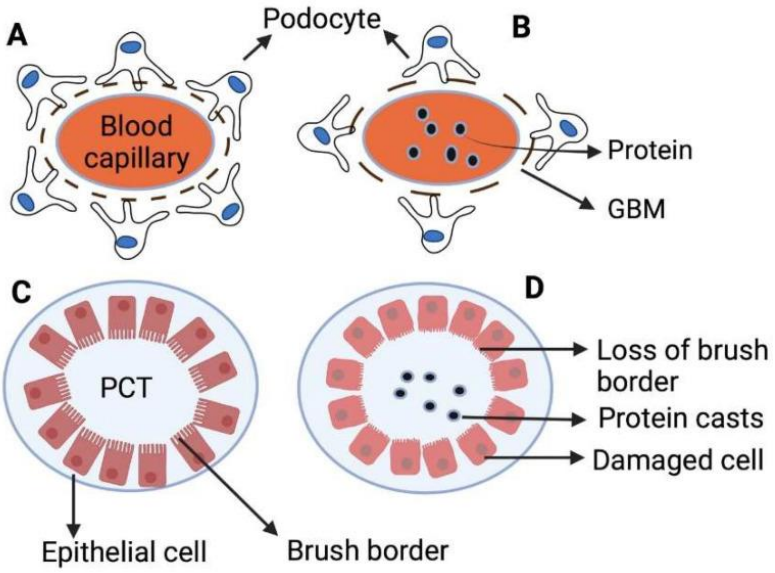

Figure 2: Schematic presentation of podocytes and proximal convoluted tubule. (A) healthy podocytes and glomerular basement membrane (GBM), (B) swollen proximal convoluted tubule (PCT) in injury condition explicit by the gaps in GBM, (C) healthy proximal convoluted tubule with good brush border epithelium, and (D) injured proximal convoluted tubule with lack of brush border.

KIDNEY DRUG DELIVERY BARRIERS

All drug delivery strategies aim to maximize therapeutic effect by delivering the medication (either passively or actively) to the targeted spot in the body while reducing buildup of the drug off-target. Following drug delivery, the medication first travels through the circulation, builds up at the intended location, and then, at a specific concentration, begins to have its therapeutic effect [45]. Following medication administration, many obstacles may prevent the drug molecules from reaching their areas of action, depending on the route used. First, during the first-pass effect, several medications taken orally are mostly rendered inactive before they reach the site of action.

The liver and small intestine are the main organs involved in drug metabolism, where medicines undergo chemical modifications to increase their water solubility and allow excretion [46]. This primarily shortens the drug's half-life and/or pharmacological activity. Second, the drugs must contend with intravascular enzymes that can break down the active components, such as nucleases and proteases, which are present in the bloodstream [47]. Furthermore, therapeutic molecules with sizes less than 6 nm have extra-short renal exposure periods because they can be eliminated by renal filtration, which could not be enough to have the desired therapeutic effect [48].

Subsequently, even therapeutic medicines that are sufficiently absorbed by the kidney still have extrarenal side effects. Additionally, a drug's intrarenal transport may not be the best for the kidney's target cell, which would decrease the effectiveness of the medication. Furthermore, some pathological diseases such as proteinuria, aberrant tubular secretion, and/or glomerular filtration might disrupt the normal renal distribution of therapeutic drugs [49]. Thus, kidney-specific medication targeting may be a compelling strategy for resolving these problems and raising the drug therapeutic index. Furthermore, pharmacological tools that are useful for clarifying the mechanisms of drug action in the kidney may be developed by cell-specific drug targeting inside the kidney.

DELIVERY SITES OF RENAL DRUG DELIVERY SYSTEMS

The hub for blood filtration, the glomerulus, is made up of a web of microcapillary tufts and mesangia that sustain the tufts' structural integrity. The glomerular filtration barrier (GFB), which is made up of podocytes, GBM, and fenestrated glomerular endothelial cells (GECs), filters blood through the glomeruli [57]. Depending on where in the cell the damage occurs, glomerulonephritis—an inflammation of the glomeruli—can take many different forms [58]. In addition to improving medication efficacy, targeted treatment to the wounded tissue can also lessen the likelihood of serious adverse effects [44]. The size exclusion features of each barrier are the primary determinant of targeting distinct glomerular cells (Figure 3). medicament delivery methods aimed at the glomerulus, arranged by location of target.

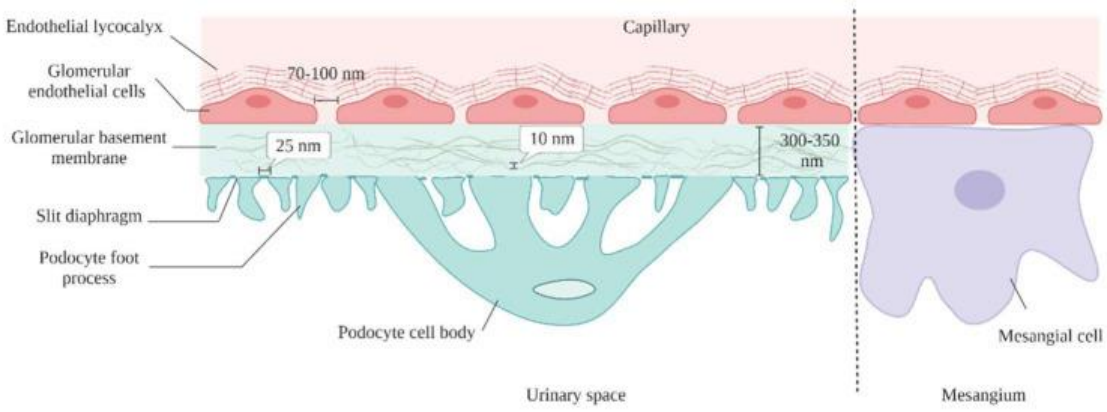

Figure 3: Schematic presentation of the glomerular filtration barriers.

7.1. Glomerular Endothelial Cells

The endothelium layer contains transcellular windows known as fenestrae, which have a diameter of between 70 and 100 nm and permit the passage of water and tiny molecules while obstructing the passage of larger things. Apart from size-based filtering, the endothelium glycocalyx within the fenestrations is essential for filtering the components of the circulating plasma according to their carrying charge [59]. The endothelial glycocalyx is a negatively charged, carbohydrate-rich gel-like structure made up of membrane-bound proteins, "proteoglycans," like glypicans and syndecans, cell surface receptors, "glycoproteins," like integrins and selectins, and long, linear polysaccharides, "glycosaminoglycans (GAGs)," which are distinguished by their strong negative charge, such as heparan sulfate, chondroitin sulfate, and hyaluronic acid [60].

7.2. Glomerular Basement Membrane

Lamina rara interna adjacent to endothelial cells, lamina densa in the center, and the outermost lamina rara externa near to podocytes make up the core, non-cellular trilaminar membrane that is known as the GBM [65]. GMB is an extracellular matrix made up of 144 different proteins that are released by GECs and podocytes [66]. Collagen subtypes (α3, α4, and α5), laminin (α5, β2, and γ1), nidogen, and heparin sulfate proteoglycan (agrin and perlecan) are the most prevalent ones in normal GBM [67]. These proteins create a network of fibrils with meshes ranging in diameter from 4 to 10 nm [62].

7.3. Podocytes

The primary filtration barrier in the glomerulus is made up of highly specialized epithelial cells known as podocytes, sometimes known as visceral epithelial cells. Interdigitating foot processes with slit diaphragms anchored in between the neighboring foot processes and a width of approximately 25 nm are distinctive

structural characteristics of podocytes [71]. Podocytes adhere to GBM via a particular protein matrix (e.g., VCAM-1, tenascin-C) and cell-cell adhesion (e.g., vinculin, E-cadherin, and nephrin) [72].

CHAPTER 8 NANOPARTICLE FACTORS FOR ENHANCED RENAL ACCUMULATION

8.1. Nanoparticle Size

The size of NPs significantly affects their biodistribution and therapeutic potential because of the size selectivity of the glomerular filtration barrier [85]. The total threshold in healthy kidneys is thought to be between 30 and 50 kDa, or 8 and 10 nm, for NPs to cross the glomerular filtration barrier. Particles of a size below this threshold can pass through the glomerular filtration barrier, enter the tubule system, and are rapidly removed by renal excretion and phagocytosis, even if smaller NPs may be able to reach deeper into tissues [80,86]. Research examined the biodistribution of 1–10 nm-sized nanoparticles and found that 24 hours after injection, the renal clearance was greater than 40% of the administered dosage (ID) [86,87,88,89,90,91,92]. For example, 2.4 ± 0.5 nm silicon nanoparticles were ~100% eliminated into the urine 24 hours after injection, according to Singh et al.'s findings [87].

8.2. Nanoparticle Surface Charge

Human glomerular vascular capillary walls function as a charge-selective barrier to block charged molecule filtration, which controls the distribution of NPs inside the kidney biodistribution [108]. Even though 1–10 nm tiny NPs are small enough to pass through the GFB, it was discovered that the interaction of nanoparticles with differing charges was influenced by the GFB's charge selectivity. Because of electrostatic repulsion, it was shown that positively-charged NPs cross the GFB more readily than negatively-charged NPs. In contrast to anionic mercaptosuccinic acid-capped quantum dots with a zeta potential of −52 mV, cationic polyethylenimine-conjugated quantum dots had a kidney accumulation of approximately 15% ID/g 24 hours after injection [105]. This was despite the fact that both particles had hydrodynamic sizes of less than 6 nm. The potential interactions between NPs and serum proteins and the interactions between NPs and the glomerulus's capillary wall are the two most important factors that influence how surface charge affects renal filtration [109]. Serum protein adsorption on NPs causes an increase in hydrodynamic diameter, which lowers renal filtration.

8.3. Nanoparticle Shape

The architecture and features of NPs, including as rheological dynamics, cellular absorption, and drug loading capacity, have been greatly impacted by the adage "form follows function" [117,118,119]. Different NPs have been produced in different forms. While certain forms, like sheets, disks, and chips, have two lateral dimensions larger than the third, other shapes, like rods, wires, and fibers, only have one long, non-nano scale dimension [120]. Oblate-shaped NPs have a longer shelf life in circulation than spherical NPs [121]. Higher fluid shear stresses are experienced by the opposite free end of an NP with a high aspect ratio when it interacts with macrophages; as a result, the NP can be removed from the cell surface before endocytosis and internalization by cells [122].

8.4. Material Choice of Nanoparticles

There have been claims of varying renal accumulations for NPs generated from different materials. Silica nanoparticles, for instance, have a high renal clearance rate and a limited targeting ability among low material density metal NPs <5 nm. This tendency is associated with the circulation rate of ultrasmall metal NPs in blood that is dependent on density [90]. Compared to NPs with a lesser density (<10 g/cm3), NPs with a larger density of above 10 g/cm3 have a stronger buoyancy force to the endothelium and may get there more rapidly [132]. Because of this, the densest NPs leave the blood vessel central flow lines, which have the highest fluid velocity [90]. Conversely, lower density NPs circulate more quickly and are more readily distributed throughout the body, which results in a shorter blood retention time and, thus, higher

renal clearance. In contrast, gold nanoparticles with a hydrodynamic diameter of 2.5 nm and a density roughly eight times higher showed two-fold lower renal clearance at 24 h after injection [133]. For example, silicon nanoparticles with a hydrodynamic diameter of 3.3 nm and low density had almost complete renal clearance (98%) at 24 h injection dose [87].

CHAPTER 9 STRATEGIES OF RENAL DRUG DELIVERY SYSTEMS

9.1. Small Molecule Prodrugs

In terms of pharmacology, prodrugs are inactive variations of a parent drug molecule that arise via transient chemical changes to bioactive substances that are activated at a particular target location to provide a medicinal effect. Prodrugs should ideally be resistant to enzymatic breakdown while remaining stable in the bloodstream and quickly changing into an active form at the site of action [134]. Usually, the goal of the chemical alteration is to increase membrane permeability or solubility while decreasing the toxicity of the drug molecules [135]. They usually consist of a tiny molecular inactive substance coupled as a lipophilicity booster or transporter to a macromolecular carrier [136].

9.2. Antibody Modified Carriers

Because of their large molecular weight (about 150 kDa), antibodies cannot be filtered by the glomerulus and, as a result, they cannot be used as a drug delivery mechanism to target the renal proximal tubuli. However, according to research on anti-cancer therapy, radiolabeled end products of antibody fragments demonstrated sustained renal radioactivity, as did radiolabeled monoclonal antibody fragments, which accumulate in renal tubuli [154,155,156]. While using antibody fragments as a renal carrier system may be advantageous, the extended and increasing buildup of fragments in the kidneys are unfavorable side effects of these cancer therapy options. Targeting disease-related growth factor receptors, such as TGF-β and EGF receptors, which are found in proximal tubular cells on their basolateral and apical membranes, is one benefit of introducing antibody fragments for therapeutic administration into these cells [157,158].

9.3. Macromolecular Carriers

When it comes to delivering therapeutic compounds to the kidney, where low molecular weight glomerular protein (LMWP) can collect in the kidneys preferentially, macromolecular carriers are thought to be highly helpful vehicles. Small molecular weight (MW <30,000 Da), physiologically active proteins found in the circulatory system, such as peptide hormones like insulin, immunological proteins like light chain immunoglobulin, and enzymes like lysozyme, are typically classified as macromolecular carriers [44]. The encapsulated drug's molecular weight is often smaller than that of the macromolecular carriers, and the protein carrier's kinetics are generally better than the drug's intrinsic kinetics. LMWP is specifically filtered via the glomerulus and reabsorption takes place through the renal tubules.

9.4. Water Soluble Polymeric Carriers

Water soluble polymers are advantageous for kidney-targeted drug delivery strategies, according to a number of studies. Any polymer's build-up in the renal tubule is primarily determined by a number of factors, including the polymer's ultimate molecular weight, kind of monomeric unit, anionic group, and anionic monomer concentration [165]. As an illustration, the low molecular weight drug polyvinylpyrrolidone (PVP) is eliminated in the urine and does not build up in the kidneys [166]. In contrast to sulfonated PVPs, which cause around 30% of the injected dosage to be detected in renal tubules, mostly the proximal tubular epithelial cells, intravenous administration of carboxylated PVPs demonstrated a better renal accumulation in the research by Kodaira et al. [167].

9.5. Nanoparticles

Nanoparticles' unique size has been widely used to create efficient targeted delivery systems. Because they can cross the glomerular filtration barrier, particles and colloids sized 5-7 nm can be employed to target the tubular region. Systems that vary in size from 30 to 150 nm do not normally enter primary urine, unless there is disease-induced disruption to the glomerular filtration barrier or the particles have been broken down into smaller sizes than 10 nm [55]. The maximum glomerular accumulation was found to occur at a particle size of 80 nm, with a few exceptions noted [170]. These exceptions included the unique chemical makeup of each carrier system and extra-small carriers (2 nm) that have trouble passing the glycocalyx and are typically eliminated by the liver.

9.6. Liposomes

Because of their controlled release profile, stability both in vitro and in vivo, targeted administration, and disease site localization, liposomes are utilized as a drug delivery platform. Liposomes are employed in a number of currently marketed products and have been the subject of much research on medication delivery. Unilamellar vesicles (SUVs) carrying methotrexate [(MTX) SUVs] connected to Dal K29 were produced by Singh et al. [182]. Following a two-hour incubation period, the vesicle's binding to CaKi-1 cancer cells (human kidney) increased about eight times more than that of unlinked (MTX)SUVs and approximately six times more than that of nonspecific mouse myeloma IgGl-linked (MTX)SUVs. Furthermore, as demonstrated by the colony inhibition assay findings, the produced system inhibited the growth of CaKi-1 cells 40 and 5 times better than free MTX and Dal K29-MTX, respectively.

9.7. Hydrogel

Different therapies that are helpful in the treatment of renal disorders can be encapsulated in hydrogels. The categories of current renal-targeted drug delivery hydrogels are as follows: (1) therapeutic-loaded for controlled release; (2) cell-seeded to increase paracrine activity and cell survival; and (3) hydrogel/NPS composites (e.g., micelle- and exosome-loaded hydrogels). The most common method of administering hydrogels for kidney treatment is intrarenal/intracapsular injection. Recent advances in the use of hydrogels for kidney drug delivery have led to an increase in the popularity of intracapsular injection, which has been shown to be successful in achieving local and controlled release of therapeutics as well as in preserving and enhancing the effects of concurrently transplanted pro-regenerative cells. But most hydrogels that have been reported on have been employed for invasive injection administration of cell treatment [175].

CHAPTER 10 CONCLUSION

Because nanomedicine is developing so quickly, certain nanomaterials have made their way into the clinical scene. Controlling medication concentrations and optimizing renal therapeutic impact while reducing toxic and other adverse drug side effects is the ultimate objective of kidney-targeted treatment design. Excellent control over particle size, charge, shape, and surface properties is provided by the nanodrug delivery system, enabling targeted treatment of a variety of kidney pathologies. In order to provide theoretical underpinnings for kidney disease treatment, this review clarified the mechanisms and methods of kidney-targeted nanodrugs with reference to the features and anatomical structure of the kidney. Strong evidence has been shown by nanotechnology for kidney-targeted drug delivery to treat a range of illnesses. The related drawbacks, however, should be managed. These include the high cost, limited yield, potential toxicity to organs other than the target, low targeting effectiveness, and poor in vivo stability. Research on kidney-targeted drug delivery systems is now primarily concerned with improving targeting efficiency and finding suitable carriers; nevertheless, there is still work to be done on understanding the release regulations and metabolic pathways of drug delivery systems after they enter target cells. As a result of extensive research on kidney illnesses and the use of nanotechnology, kidney-targeted medicine delivery systems will be crucial in the treatment of renal ailments.

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