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Carbon quantum dots as transcutaneous drug carriers: mechanisms, challenges and prospects

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Incorporation of nanoparticles has revolutionized drug delivery by optimizing the targeted transport of drugs, boosting the solubility and stability of pharmaceuticals, and facilitating precise, controlled release. These breakthroughs have made a significant contribution, especially in personalized medicine for many health issues. A variety of nanoparticles, including lipid-based systems, polymeric carriers, dendrimers, metallic nanoparticles, and nanogels, have been employed in drug delivery to improve drug solubility, protect active compounds from degradation, and achieve controlled release. Quantum dots are zero dimensional nanoparticles distinguished by intrinsic fluorescence, in particular carbon quantum dots allow for real-time imaging, superior biocompatibility, and antimicrobial properties rendering them highly adaptable for sophisticated therapeutic and diagnostic uses. Transcutaneous drug delivery devices offer a non-invasive approach for administering medications through the skin, enabling drugs to bypass the gastrointestinal tract and first-pass metabolism thereby improving bioavailability, and promoting enhanced patient compliance. Nanoparticles, particularly those sized between 1 and 10 nm in all dimensions, significantly enhance skin penetration, thereby improving drug delivery to deeper tissues, thus making carbon dots an ideal candidate as a nanocarrier in the transcutaneous system. A focused review on carbon quantum dots as novel nanocarriers to overcome present obstacles in transcutaneous drug administration is critically presented.

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1 Introduction

Administration of drugs can be through various routes: oral, buccal, sublingual, transcutaneous, intravenous, and nasal routes.[1] Among these, transcutaneous drug delivery (TDD) represents a non-invasive method that circumvents the gastrointestinal system and first-pass metabolism, improving patient adherence, enhancing bioavailability and allowing targeted therapeutic activity.[2] Nanoparticles play a pivotal role in drug delivery as they improve the solubility, stability, and targeted transport of therapeutics, allowing for controlled and precise release with reduced systemic side effects. Their capability to transport across biological barriers and be functionalized with target tissues makes them key for modern, personalized treatments for a broad range of diseases.[3,4] Incorporation of nanoparticles in transcutaneous drug delivery systems (TDDS) can effortlessly overcome limitations such as selective permeability. The unique physicochemical properties of the nanoparticles – such as their optical and magnetic characteristics, inertness, stability, low toxicity, biocompatibility, ease of functionalization, high cellular uptake efficiency, and non-immunogenic response – make their incorporation with TDD a potential research area.[5] Different nano systems, including nanogels, polymeric nanoparticles, metal nanoparticles, dendrimers, micelles, lipid nanoparticles, carbon-based nanoparticles (CNPs) and quantum dots, effectively permeate the epidermal barrier without causing tissue damage.[6] CNPs can be classified as carbon nanodots (CNDs), carbon nanotubes (CNTs), carbon polymeric dots (CPDs), and carbon quantum dots (CQDs). CNDs are spherical CNPs whose particle size is greater than 10 nm in diameter. They tend to have a more disordered or amorphous carbon core and their fluorescence properties are usually promoted by surface defects, as opposed to size.[7] CNTs, one dimensional CNPs, have been explored for TDDS due to their higher drug loading capacity and structure.[8] But one of their significant drawbacks is toxicity which can induce oxidative stress, inflammation, and cytotoxicity.[9] CPDs are a hybrid nanoparticle formed by the use of a carbonized core and a vast shell made of polymer chains, where cross-link enhanced emission is a key optical characteristic.[10] Whereas CQDs – zero dimensional CNPs with quasi-spherical structure and a crystalline core of sp^2/sp^3 hybridized carbon – have size-dependent photoluminescence as a result of the quantum confinement effect.[11] The small size of carbon quantum dots (CQDs) is more advantageous compared to larger carbon-based nanoparticles due to the fact that it enables deeper penetration through the skin, increased cellular uptake, and reduced immune clearance, all of which enhance transcutaneous drug delivery efficacy.[12] Although these three are highly soluble and non-toxic, CQDs have a distinctly defined crystalline structure and a consistent connection between their size and electronic configuration.[13] Thus, making them a better candidate for theranostics applications. The size of CQDs, particularly those less than 10 nm, plays a significant role in enhancing the effectiveness of drug delivery.[14,15]

Over time, TDD has been employed to induce local pharmacological actions on the tissue of the skin. Drugs travel through the intact stratum corneum (SC) of the epidermis, to reach the interfollicular space through passive diffusion of neutral molecules.[16] The drug molecules initially diffuse to a target organ before being released into the systemic circulation where they affect the related tissue and exert a therapeutic effect.[17] In transcutaneous drug delivery for localized therapy, drug molecules diffuse into the skin and then into the capillaries of the dermis, minimizing their entry into the systemic circulation. The outer skin layer SC, is selectively permeable and

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permits the entry of small lipophilic chemicals but prevents the passage of larger or hydrophilic molecules, thus rendering TDD challenging.[18] Overcoming this barrier demands methods like penetration enhancers or physicochemical drug modifications to maximize permeability and ensure effective delivery.[19] TDDS face numerous limitations, including limited use for highly potent low molecular weight drugs, poor release rates for conditions needing a quick onset of therapy, and skin permeability issues.[20] In addition, patients can experience skin irritation or dermatitis due to enhancers and excipients, and there is a risk of systemic toxicity due to the high drug loading in patches. The process is costly and challenging to deliver large amounts, whereas tolerance-causing drugs require close monitoring to avoid undesirable side effects.[21]

In order to overcome the challenges of TDDS, incorporation of nanoparticles is of significant relevance, particularly CQDs, whose special structures, large surface area, biocompatibility, simple availability, and surface modifiability make them extremely crucial in drug delivery for promoting targeted administration as well as interactions with biological systems. Nanoparticles are able to enhance skin permeability by weakening the SC barrier or by serving as carriers that facilitate the transdermal passage of larger molecules.[22] Besides, nanoparticles have the ability to provide controlled release profiles, which reduces the risk of systemic toxicity and enhances the efficacy of treatment.[23] Cellular uptake through endocytosis is increased by smaller CQDs, allowing deeper penetration into tissues, and prolonging systemic circulation through avoidance of rapid clearance by the reticuloendothelial system.[24] Their high surface area-to-volume ratio allows for increased drug loading capability and sustained release, in addition to enabling effective surface functionalization with targeting ligands, ensuring precise and safe therapeutic delivery. In diagnostics, CQDs offer durability in fluorescence, making them highly suitable for bioimaging and biosensing applications. Their sensitivity to pH changes and specific ions enable identification of disease-specific biomarkers, and their application in electrochemical biosensors enables real-time monitoring of biological processes, such as the activity of neurotransmitters. These features make CQDs powerful tools for improving medical diagnostics and treatment.[25,26] Their anti-inflammatory and antioxidant properties assist in the regulation of oxidative stress and inflammation, therefore, avoiding skin irritation or dermatitis. Recent research in this field emphasizes their potential in the creation of enhanced TDD applications, which require sufficient attention of fundamental scrutiny to applications. This review article highlights recent developments in TDDS using CQDs as nanofillers that have demonstrated how their unique physicochemical properties can enable them to find theragnostic uses, as well as future opportunities of fine-tuning these systems to maximize their therapeutic accuracy and efficacy in a wider range of medical therapies.

2 Drug delivery mechanism in transcutaneous systems

The skin, the body's biggest organ, spans 2 m^2 and constitutes 15% of total body weight.[27] It comprises the SC and the viable epidermis (VE). The SC, measuring 10–20 μm in thickness, consists of keratin-rich corneocytes and a lipid bilayer, creating a "brick-and-mortar" architecture (lipid bilayer) that serves as the skin's barrier. The VE, measuring 100–150 μm in thickness, comprises proliferating keratinocytes that generate the SC by keratinization and secrete cytokines and chemokines to facilitate immunological activity.[28]

Lying beneath the epidermis, the dermis is around 1200 μm thick and comprises connective tissue like fibronectin, collagen, elastin, and glycosaminoglycan matrix.[29] It contains sweat glands, sebaceous glands, hair follicles, nerve endings, and blood and lymphatic arteries. Bypassing SC, hair follicles and sweat ducts offer a direct route from the dermis to the surface, acting as an appendageal pathway for skin penetration. Underneath the dermis, the subcutaneous "fat" tissue is made up of loose connective and adipose tissue that supports and

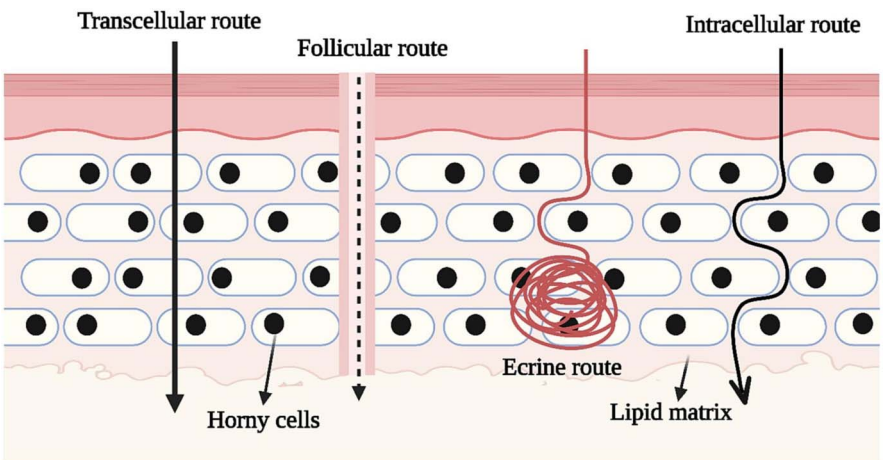

Fig. 1 A schematic representation for different routes through which drugs penetrate into the skin tissue (reproduced from ref. 18 copyright 2024, with permission from Elsevier).

connects the muscles and skin. Collagen and fat-filled cells connect the dermis and epidermis to deeper tissues.[30]

Transcutaneous conveyance transpires *via* three primary pathways: intracellular, transcellular, and appendageal,[31] as shown in Fig. 1. The intracellular route, the principal pathway, entails nanocarriers traversing intercellular lipids by diffusion.[32] Flexible nanocarriers, particularly those based on polymers, have superior efficacy compared to rigid nanocarriers, such as metal nanoparticles, in this pathway. The transcellular pathway is more rapid and complex, since the nanocarriers must cross both lipophilic and lipophobic barriers within skin cells; amphiphilic nanocarriers may facilitate this process. The appendageal pathway, which entails penetration through hair follicles and glandular ducts, is infrequent owing to the limited surface area of these structures. Nonetheless, diminutive nanocarriers (about 20 nm) have demonstrated the ability to penetrate more profoundly and facilitate prolonged medication release, specifically aimed at hair follicles; thus, CQDs are an ideal candidate as a nanocarrier for TDDS owing to their extremely small size as well as their amphiphilic nature after surface functionalization.[14] Each pathway presents chances for transcending the epidermal barrier, necessitating the optimization of nanocarrier characteristics for the selected route.[33]

3 Enhancing transcutaneous drug delivery efficiency

Despite the advantages, TDDS has constraints in administering a diverse array of active compounds due to factors like low molecular weight, short half-life, elevated permeability, ideal oil/water partition coefficient, and low melting point. Molecules adhering to Lipinski's Rule of Five are optimal for TDDS, indicating that medicines with molecular weights below 500 Da and defined limits for hydrogen bond donors and acceptors demonstrate enhanced penetration.[34] Although small lipophilic compounds often exhibit high efficacy, certain small hydrophilic molecules can penetrate the epidermal barrier through the transappendageal pathway. Nonetheless, substantial molecules such as proteins and peptides, generally over 500 Da, encounter difficulties in traversing the skin barrier owing to its tight connections and intricate architecture.[35]

To address these constraints, a range of permeation enhancement techniques are employed, encompassing chemical, physical, biological procedures, and prodrug tactics.[36] These approaches are classified into active and passive types. Active approaches utilize external stimuli such as mechanical or electrical pressures to enhance drug delivery, whereas passive methods depend on chemical enhancers and innovative carriers to improve drug permeability and solubility, frequently leading to prolonged release.[37] These methodologies have been effectively utilized for numerous pharmaceuticals, accompanied by continuous advancements and patents inside the domain.

3.1 Active techniques

Active methods including sonophoresis, iontophoresis, electroporation, microneedles (MNs) and jet injectors as shown in Fig. 2, either use gradient field-induced convective flow to increase drug penetration or speed up drug particles into the skin.[38] Iontophoresis facilitates drug penetration through the skin by means of electro-osmosis for both neutral and charged medicines and electrorepulsion for charged molecules. Skin surface exposure, length, and current magnitude are factors that affect iontophoretic delivery.[39,40] Research indicates that when paired with chemical enhancers such as borneol or microneedle arrays, iontophoresis dramatically improves medication penetration.[41] To improve drug penetration, sonophoresis, also known as phonophoresis, uses ultrasonic waves with frequencies ranging from 20 kHz to 16 MHz.[42] Low-frequency sonophoresis (20–100 kHz) has been shown in studies to enhance medication penetration, with further advantages noted when paired with nanoparticle carriers.[43]

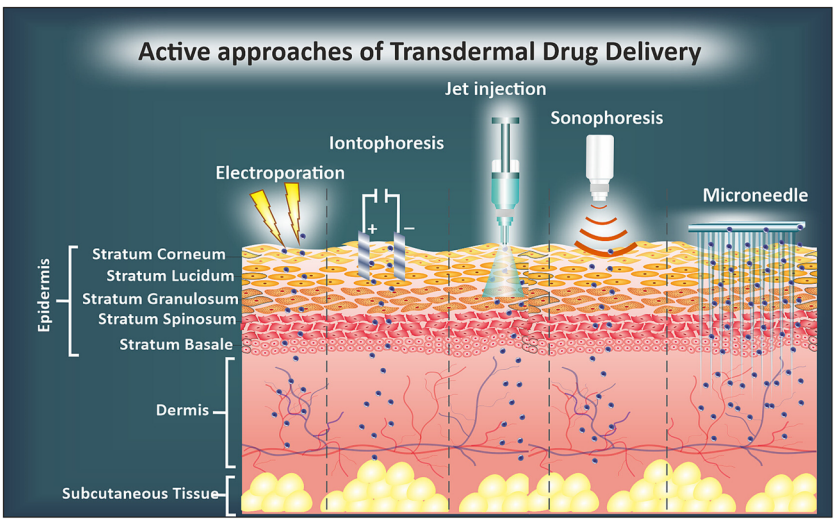

Fig. 2 Various active techniques used in TDDS (reproduced from ref. 45 copyright 2022, with permission from Elsevier).

Cavitation, temperature effects, convective transfer, and mechanical stress are some of its mechanisms. Advancements in sensor technology are improving the potential of sonophoresis for delivering medication through the skin, despite limited research on the topic.[44,45] Electroporation uses high-voltage electrical pulses to transiently rupture the lipid bilayer of the skin, facilitating the introduction of therapeutic substances, such as large hydrophilic molecules like insulin and DNA. The efficacy of this approach is contingent upon the pulse characteristics (voltage, duration, frequency). Research indicates that electroporation markedly improves drug penetration relative to passive delivery, presenting a viable alternative for insulin administration.[46,47]

Microneedles are diminutive needles that form microchannels in the dermis for the administration of pharmaceuticals. They are less intrusive and devoid of pain in comparison to hypodermic needles.[48] Diverse categories of MNs (solid, hollow, coated, polymer, dissolving, hydrogel-forming and jet injectors) have been engineered for distinct uses.[49,50] Metal nanoparticles have been utilized in therapies for skin cancer, rheumatoid arthritis, and medication targeting, demonstrating enhancements in stability, cellular absorption, and anti-inflammatory properties.[51–53] External cues, such as light, can also influence them for enhanced control of medication release. Similarly, another innovation in TDDS is needleless jet injectors which administer medications such as insulin or vaccines *via* high-pressure jets that penetrate the skin without the use of a needle. This technique provides benefits such as painless administration, enhanced bioavailability, and less chance of damage.[54,55] Jet injectors are commercially utilized for insulin administration, with research indicating they can lower glucose levels more rapidly than conventional insulin injections. These devices remain under examination for enhancement.[56]

3.2 Passive techniques

Passive methods for enhancing transdermal permeation involve the use of various chemical agents that interact with the skin's SC to weaken its barrier, allowing drugs to penetrate more effectively. Common permeation enhancers include alcohols, fatty acids, amides, surfactants, and terpenes. First generation enhancers, although effective, can cause irritation, allergies, or toxicity. To mitigate these issues, bioenhancers such as phospholipids, essential oils, and enzymes are preferred.[45,57] Nevertheless, further efficiency can be brought into TDD by advanced drug carriers such ethosomes, dendrimers, transferosomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), microemulsions, and liposomes,[45,58] as represented in Fig. 3. Although surfactant-induced irritation is still a problem, microemulsions made of water, oil, and surfactants improve permeability and solubility.[58] While NLCs further increase drug loading and controlled release, SLNs, which are composed of lipids and surfactants, offer stability and boost drug penetration.[59–62] The nanoscale architecture of dendrimers enhances drug solubility and controlled release, whereas the flexible nature of transferosomes permits deeper skin penetration.[63,64]

Additionally, ethosomes and liposomes are essential for sophisticated transcutaneous administration.[65,66] PEGylation and other changes enhance the stability of liposomes, which are made of phospholipid bilayers and may transport both hydrophilic and lipophilic medicines.[67,68] Ethosomes are more effective than conventional liposomes because of their high ethanol content, which allow deeper penetration by rupturing the epidermal barrier.[69] These nanocarriers are shown in Fig. 3. When compared to traditional formulations, studies on these carriers have shown better drug penetration and bioavailability, underscoring their potential for improved therapeutic results.

Beyond lipid-based systems, recent advancements have extended to various nanomaterials that offer unique advantages for transcutaneous drug delivery. Metallic nanoparticles (NPs), including silver (AgNPs) and gold (AuNPs), are being used for transdermal medication administration because of their enhanced ionic conductivity, high surface-to-volume ratio, and capacity to penetrate skin barriers. Gene therapy and targeted delivery are made possible by the ability to functionalize AuNPs, which range in size from 3 to 120 nm, with peptides, proteins, and nucleic acids. These nanoparticles have demonstrated the capacity to permeate the skin and access deeper layers such as the epidermis and dermis.[6,70,71] Ag NPs, recognized for their extensive antibacterial characteristics, are increasingly attracting interest in dermatology.[72] Moreover, metal oxide nanoparticles such as TiO_2, ZnO and Fe_3O_4 utilized for their ultraviolet-absorbing characteristics, encounter issues including phototoxicity and the production of reactive oxygen species, which restrict their application.[5,73–76] Silica nanoparticles, including adjustable pore dimensions, are investigated for their drug-loading potential and dermal absorption, while toxicity issues persist.[77] Quantum dots (QDs), semiconductor-derived nanoparticles, exhibit distinctive fluorescent characteristics for monitoring medication distribution; yet, they pose safety concerns, particularly due to their cadmium composition.[78]

Metallic nanoparticles, regardless of their promise in medication delivery, pose numerous substantial obstacles. They can be deleterious, inducing oxidative stress and cellular damage upon accumulation in the body.[80] Furthermore, they may elicit

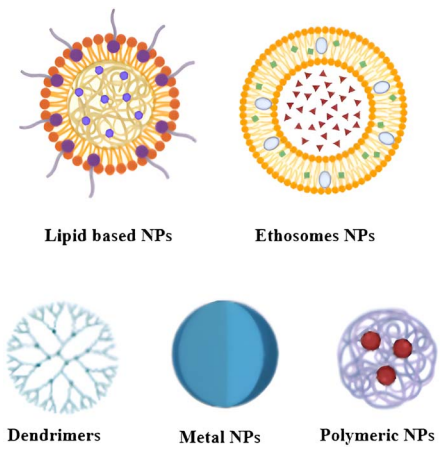

Fig. 3 Different nanocarriers used in passive techniques for TDDS.

inflammatory reactions, resulting in discomfort or negative effects, especially in susceptible individuals. The permanence and toxicity of environmental substances elicit further concerns, leading to regulatory examination.[81] CNPs have numerous features that render them particularly advantageous for various applications. Their distinctive structural configurations and hybridizations confer specialized features suitable for applications in electronics, biology, and optoelectronics. CNPs, especially fullerenes and certain carbon nanotubes, demonstrate significant biocompatibility, rendering them appropriate for medicinal and cosmetic applications, particularly in dermatology. Their elevated surface area improves interactions with biological systems, facilitating medication administration and biosensing. Their surfaces can be readily modified for specific and tailored uses. These characteristics, along with their present application in cosmetics and biosensors, highlight their increasing importance in the health and technology industries.[9] Table 1 provides an overview of different nanocarriers used to improve skin penetration in TDDS, outlining their main characteristics, functions, and relevant references.

Given their promising properties, particularly in drug delivery and dermatological treatments, understanding the limitations associated with the size of CNPs is critical for effective application. Despite their ability to traverse the stratum corneum and localize within hair follicles, nanoparticles larger than 10 nm face challenges in permeating deeper layers of the skin. Particles within the 30–60 nm range often show reduced cellular uptake due to inefficient receptor-mediated endocytosis and are prone to rapid clearance by the mononuclear phagocyte system, thereby limiting their circulation time and sustained drug delivery potential. While they may enhance drug retention at the surface, this can also elevate the risk of localized toxicity.[79] Therefore, optimizing nanoparticle size is essential to balance skin penetration, immune system avoidance, and drug-loading efficiency, particularly when designing carbon-based nanomaterials for transcutaneous therapeutic applications. CQDs are thus the best CBNs compared to their counterparts owing to their diminutive size, biocompatibility, lower cytotoxicity, better fluorescence and enhanced physicochemical properties.

4 Significance of surface modification of CQDs

Surface modification (SM) of CQDs has transformed these materials from simple fluorescent nanoparticles to multifunctional ones with advanced applications across different fields of science. The surfaces of these CQDs have abundant functional groups such as carboxylic, hydroxyl and amine, making their SM easy, allowing control over their physicochemical properties. This surface engineering is done through covalent bonding and non covalent bonding.[82]

Covalent bond based surface engineering of CQDs will result in strong chemical bonds between the surface functional groups and outside molecules, which provides high stability and prolonged functionality to the CQDs, but with potential modifications to the electronic structure of CQDs. CQDs with abundant carboxyl groups are treated with amino groups to

Table 1 Different nanocarriers for skin penetration enhancement

Nanocarriers	Key features	Role in TDDS	References
Ethosomes	Phospholipid vesicles with high ethanol content	Fluidizes SC lipids, improves deep skin penetration for hydrophilic and lipophilic drugs	72
Dendrimers	Highly branched, tree-like polymers with functional surface groups	Improve solubility, controlled release, and facilitate targeted delivery across skin barrier	65
Transferosomes	Ultra-deformable liposomes containing edge activators (*e.g.*, surfactants)	Enhance penetration and systemic delivery of larger molecules	58
Solid lipid nanoparticles	Solid lipid core stabilized by surfactants	Enable controlled release, improve drug permeation and protect drugs	62
Nanostructured lipid carriers	Blend of solid and liquid lipids, creating an imperfect lipid matrix	Higher drug loading, controlled release, and better skin penetration compared to SLNs	45
Microemulsions	Thermodynamically stable mixtures of oil, water, surfactant, and co-surfactant	Enhance solubilization and diffusion of drugs through the SC	79
Liposomes	Phospholipid bilayer vesicles enclosing an aqueous core	Deliver both hydrophilic and lipophilic drugs	45
Inorganic nanoparticles (Au, Ag, Zn, SiO_2, Fe_3O_4)	Unique optical, magnetic and catalytic properties	Enhance permeation, enable photothermal or photodynamic therapies, and offer imaging capabilities	5
Carbon based nanoparticles (CNTs, GO, CQDs)	High surface area and functionalization potential	Improve skin penetration, enable high drug loading, provide controlled release, and support theragnostic applications	9

refine their fluorescence properties and thus improve their bioimaging capabilities. Surface polarity can be controlled with esterification, thus making the surface of CQDs more lipophilic.[83] The relatively weak forces like electrostatic forces, hydrogen bonding, van der Waals forces, and π–π stacking, governs non-covalent SM of CQDs, which despite their reversibility and weaker strength than covalent bonds, allows the preservation of the intrinsic electronic structure and fluorescence properties of CQDs.[84]

The surface modified CQDs are of great importance in TDD, which has the major challenge of crossing the barrier of the stratum corneum. CQDs can be modified to enhance skin adhesion, intercellular and follicular pathway permeation, and colloidal stability by modulating surface functional groups through coating with polymers, charge modulation, or attaching lipophilic moieties. Surface engineering can also be used to achieve high drug-loading performance and stimulus responsive release in the skin microenvironment. The intrinsic fluorescence of CQDs, preserved through surface passivation, allows real-time visualization of skin penetration and drug distribution, making surface-modified CQDs highly promising multifunctional carriers for safe, efficient, and traceable transdermal drug delivery systems.

5 Role of CQDs in TDDS

In transcutaneous drug delivery systems, CQDs have shown great promise as nanocarriers because of their physicochemical properties which allow for both real-time imaging to tracking drug distribution and effective drug transport through the SC. Their ability to surface functionalize enables targeted delivery and accurate drug loading, and their low toxicity and biocompatibility make them appropriate for applications requiring prolonged release with little skin irritation.

5.1 Application of CQDs in TDDS for wound healing

Roy *et al.* emphasized the pivotal function of CQDs in improving a biocompatible, thermoresponsive polymeric composite film for transdermal medication administration. CQDs were obtained using pomegranate peels as their source and were integrated into a 2-cyclodextrin and poly(*N*-vinyl caprolactam) (pVCL) matrix, which significantly improved the functionality of the system. CQDs increased the drug loading capacity, and enhanced sustained and temperature-controlled drug release near their physiological low critical solution temperature (LCST), which is about 32.6 °C, and also improved the mechanical strength and surface stability of the film. They had large surface area that increased their contact with the skin thereby making them able to penetrate the skin and absorb lidocaine hydrochloride monohydrate (LHM) effectively. The fluorescence properties of CQDs enabled real time inspection of the distribution of medications. Moreover, their high biocompatibility and low toxicity ensured safe use as confirmed by *in vitro* and *ex vivo* studies. Thus, CQDs play a vital role in improving the efficacy of the formulation, which makes them vital in creating elaborate and efficient TDDS.[85]

Demirci *et al.* synthesized and characterized nitrogen-doped carbon dots (NCDs) using a hydrothermal method using citric acid and polyethyleneimine as the precursors. These biocompatible photoluminescent nanoparticles showed good optical and thermal stability, high antibacterial activity especially in the case of methicillin-resistant *Staphylococcus aureus* (MRSA), and low toxicity to mammalian cells. Characterization including Fourier transform infrared spectroscopy (FTIR), dynamic light scattering (DLS), thermogravimetric analysis (TGA) and transmission electron microscopy (TEM), validated the size (as small as 11.5 nm), surface charge and thermal stability of the system, which allowed understanding their permeation ability with skin tissues with 26.6% penetration and 15.5% retention in pig dermal tissue after 24 hours. Their fluorescence allows real-time tracking, and antimicrobial assays showed considerable effectiveness with a minimum inhibitory concentration of 0.3125 mg mL^{-1} (MRSA) and 1.56 mg mL^{-1} (*E. coli*) of the bacteria by breaking the bacterial membranes. These attributes highlight its potential in the delivery of medication through the skin, wound care and treatment of infections, and future work should focus on improving therapeutic efficacy.[86]

Positively charged nitrogen-doped carbon quantum dots (PC-CQDs) with known strong antibacterial activity against a wide range of bacteria, which include Gram-positive and Gram-negative species with maximum effect against *Staphylococcus aureus*, were synthesized by Hao *et al.* The complex antibacterial activity consists of electrostatic interaction that enhances adhesion to negatively charged bacterial membranes and disrupts bacterial gene activity, and the generation of reactive oxygen species (ROS) that cause oxidative stress leading to bacterial cell death. PC-CQD's distinct regions of inhibition and successful curtailed bacterial proliferation at lower dosage, were studied by disk diffusion and MIC experiments. Importantly, even after 30 days of consistent exposure, bacteria failed to develop resistance to PC-CQDs, hence justifying their applicability as a lasting antibacterial agent. Their therapeutic efficacy was further supported by *in vivo* studies that used infected rodent models that showed that PC-CQD-treated wounds had significantly accelerated healing compared with controls. The histological analysis demonstrated that tissue regeneration was successful and there was no significant damage to the vital organs. Moreover, the tests of *in vitro* cytotoxicity and hemolysis showed outstanding biocompatibility, more than 90% of cell survival was observed and red blood cells were not damaged.[87]

Li *et al.* fabricated a multifunctional carbon quantum dot-based hydrogel to enhance wound healing and improve antibacterial efficacy. The injectable and self-healing hydrogel, synthesized using oxidized dextran (ODex), carboxymethyl chitosan (CMCS), and gentamicin-modified CQDs, showed impressive pH-controllable swelling (up to 500%), rapid gelation (in 3 minutes) and high mechanical strength. CQDs interacted with bacterial membranes electrostatically thus producing high levels of ROS surpassing that of hydrogen peroxide to effectively inhibit bacterial growth. *In vitro* results showed significant antibacterial activity against Gram-positive and Gram-negative bacteria, such as a decrease in biofilm formation of more than 90%. The hydrogel exhibited low

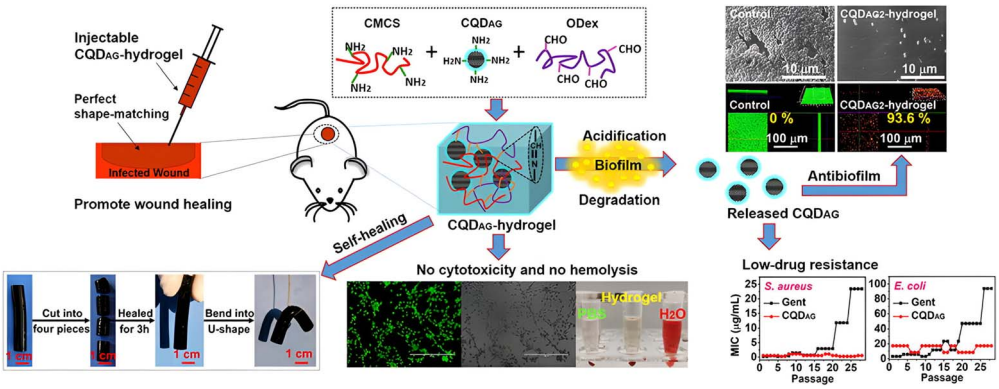

Fig. 4 A schematic illustration of CQD incorporated hydrogel for TDDS in WH (reproduced from ref. 88 copyright 2021, with permission from Elsevier).

cytotoxicity (>90% cell viability), low hemolysis (<5%) and thus confirmed its biocompatibility. *In vivo* experiments with diseased rat wound models revealed CQD hydrogel hastened wound healing and tissue remodelling with increased collagen deposition and decreased inflammation compared with controls. The results of this study indicate the therapeutic value of the hydrogel as a safe and effective wound treatment of infected wounds to reduce the possibility of antibiotic resistance, shown in Fig. 4.[88]

Antimicrobial chitosan (CS) based hydrogel was fabricated by Kazeminava *et al.* by incorporating N-CQDs synthesized using folic acid as the precursor with an aim to enhance wound healing. The CQDs are used as cross linking agents, which increase the mechanical strength, photoluminescence, and antibacterial capabilities of the CS films. Gentamicin (GM) an antibiotic was added into the matrix and sustained drug release was exhibited for up to 48 hours with a concentration dependent effect of CQD. The successful introduction of CQDs was confirmed by material characterization which concluded the increase of surface roughness and tensile strength. Blood coagulation ability and hemolysis rate also increased with the increase in concentration of CQDs. *In vitro* studies revealed more than 80% cellular viability and significant antibacterial activity, particularly against *E. coli*. The eco-friendly and cost-effective production of the CS/CQD/GM films presents great potential for biocompatible wound dressing with better therapeutic effects.[89]

Dehghani *et al.* developed a chitosan/silk fibroin (CS/SF) nanofibrous scaffold with an addition of N-CQDs as well as α-tricalcium phosphate (α-TCP) in order to enhance wound healing applications. N-CQDs were obtained through a hydrothermal reaction and integrated with α-TCP and electro spun into CS/SF mats, producing a hybrid nano-scaffold that is stronger, more hydrophilic, and biodegradable. Structural integrity of the nanofibers was confirmed by characterization, including FTIR and TGA, and biological analyses showed high antibacterial effects of *E. coli* and *S. aureus* with controlled degradation rates. The *in vitro* experiments showed enhanced cell vitality, faster fibroblast motility and beneficial cell morphology. *In vivo* experiments on a rodent model further supported the efficacy of scaffold by showing an accelerated wound healing process and increased tissue regeneration with minimum inflammation. CQDs are known to increase antibacterial properties, cell growth, mechanical and hydrophilic properties and biocompatibility of the scaffold, which makes them a key element for efficient wound healing and tissue regeneration. The combination of CS, SF, N-CQDs, and α-TCP resulted in a high-performance wound dressing that was good in the prevention of infection and tissue regeneration.[90]

Li *et al.* synthesized ginger derived CQDs (GCDs) using an innovative microwave-assisted technique, positioning them as potential agents for wound healing. Employing ginger charcoal, which has been frequently used in traditional Chinese medicine, the resultant GCDs demonstrated advantageous physicochemical characteristics, such as nanoscale dimensions (2.3 nm), hydrophilic functional groups, and stable blue fluorescence. Thorough characterization employing TEM, FT-IR, X-ray photoelectron spectroscopy (XPS), and zeta potential analysis, validated the morphology, functional groups, elemental content, and colloidal stability of the GCDs. *In vitro* and *in vivo* investigations indicated that GCDs markedly diminished inflammation, enhanced cell proliferation and migration, and expedited wound healing by inhibiting the TLR4/NF-B pathway. The study underscores GCDs as efficient, natural, and multifunctional nanomaterials for anti-inflammatory wound care applications.[91]

Wen *et al.* made a light-responsive, biocompatible hydrogel film dressing made from chitosan (CS), poly(vinyl alcohol) (PVA), and turmeric-derived carbon quantum dots (CQDs) for the efficient management of chronic wounds. CQDs were synthesized by carbonization of turmeric extract and integrated into the chitosan-polyvinyl alcohol (CS-PVA) matrix to exploit their photodynamic characteristics. The composite films were analyzed using SEM, FTIR, UV-vis spectroscopy, and mechanical testing, verifying their smooth shape, hydrogen bonding contacts, high transparency, and flexibility. CQDs were essential for the production of ROS when exposed to 405 nm light, facilitating photodynamic antibacterial efficacy. The films demonstrated pronounced antibacterial efficacy against *E. coli* and *S. aureus*, validated by colony counting and live/dead

staining, with negligible cytotoxicity. They exhibited significant swelling capacity, appropriate water vapor permeability, swift hemostatic properties, and facilitated fibroblast migration. *In vivo* investigations in infected wound models demonstrated expedited healing, decreased inflammation, augmented collagen deposition, and heightened vascularization.[92]

Liu *et al.* successfully fabricated copper-doped carbon dots (Cu-CQDs) using resveratrol which significantly enhanced the antibacterial, antioxidant, and angiogenic characteristics of bacterial cellulose (BC) membranes for wound healing. Cu-CQDs demonstrate significant antibacterial efficacy, remarkable biocompatibility with minimal cytotoxicity up to 320 μg mL^{-1}, and efficiently mitigate oxidative stress and inflammation. They additionally stimulate angiogenesis by activating the VEGF and MAPK pathways, which are crucial for tissue regeneration. Their effective incorporation into BC membranes enhances the material's mechanical strength, hydrophilicity, and stability, rendering Cu-CQDs a significant multifunctional element for advanced wound dressing applications.[93]

Zhang *et al.* developed a novel TDDS based on porphyrin-functionalized CQDs (pCQDs) using hydrothermal synthesis to address drug resistant bacterial wound infection. A strong broad-spectrum bacteria killing capability is shown by the system. The positively charged surfaces bind to the bacteria and induce bacterial membrane disruption leading to bacterial death and minimizing the development of bacterial resistance. The intrinsic red fluorescence of pCQDs helps in real time monitoring of the antibacterial activity of the system. TEM, XPS, FTIR, and energy dispersive X-ray spectroscopy (EDS) studies helped to understand the homogenous morphology, composition, and hydrophilic and positively charged surface of the system. UV-vis and fluorescence spectroscopy were used to study their optical properties which in turn helped in using them for real time monitoring of the bacterial activity. *In vitro* studies exhibited a strong bactericidal effect against Gram-positive and Gram-negative bacteria, including MRSA; and *in vivo* mouse models indicated increased wound healing, lower inflammation, and tissue regeneration over controls and antibiotics. Biosafety studies reported low toxicity and a transcriptomic study showed that pCQDs have multifaceted antibacterial effects, disrupting bacterial membrane transport, bacterial metabolism, causing oxidative stress, with an inhibitory effect on signal transduction, resulting in bacterial death *via* different pathways to the action of traditional antibiotics.[94]

Partovi *et al.* fabricated a novel nanoscaffold using gelatin, chitosan, and polycaprolactone incorporated with silver nanoparticle coated CQDs (Ag-CQDs) which was electrospun into nanofibrous wound dressings. The CQDs were prepared using a hydrothermal method using citric acid and thiourea as precursors. Incorporation of Ag-CQDs in the nano scaffold improves their antibacterial properties against both Gram-positive and Gram-negative bacteria. The morphology, size distribution, the surface chemistry, optical properties, and the successful coating with AgNPs were confirmed by characterization techniques such as TEM, DLS, UV-vis spectroscopy, photoluminescence, FTIR, and XRD. *In vitro* studies were done for antibacterial activity and *in vivo* studies for wound healing in a rat model revealed higher antibacterial activity, faster collagen deposition, less inflammation, and wound healing compared to control dressings. Histological examinations also indicated the presence of better tissue regeneration and less immunological cell infiltration. This multifunctional nanofibrous system takes the synergistic benefits of CQDs, AgNPs and citrate as a scaffold, which results in a promising skin tissue engineering platform and enhanced chronic wounds treatment.[95]

Yuan *et al.* developed a novel smearable hydrogel, incorporated with modified CQDs (mCQDs) with cellulose nanofibers (CNF), tannic acid (TA), and PVA which helps in visual intelligent wound healing monitoring and photodynamic antibacterial treatment. The mCQDs were synthesized *via* a hydrothermal method with the help of citric acid and thiourea and modified by grafting 1,2,3,4-butanetetracarboxylic acid (BTCA). The mCQDs were incorporated into the polymeric matrix since they exhibit pH-sensitive multicolor fluorescence which in turn monitor real-time wound healing status. The production of ROS under light irradiation was used as an effective antibacterial photodynamic therapy against pathogens like *S. aureus*, *E. coli*, *P. aeruginosa*, and *A. baumannii*. Optical properties, surface chemistry and nanostructure of the system were studied using TEM, XPS, FTIR, UV-vis and fluorescence spectroscopy. Self-healing, stretchability, and skin adhesion properties of the hydrogel were understood with the help of mechanical and rheological characterizations. Biological evaluations were done and it was observed that the antibacterial efficacy is good both in the dark and under light irradiation. Antioxidant activity, hemostatic effect, biocompatibility, and enhanced wound healing were observed in a mouse model and was confirmed by histological analyses. These unique attributes of the hydrogel makes them a competitive theranostic system to customized and responsive wound care and improved wound healing.[96]

Rooholghodos *et al.* developed an enhanced electrospun nanofiber wound dressing Scaffold using PVA, cellulose nanofibrils (CNFs), CQDs, Fe_3O_4 NPs, and rosemary extract (RE). CQDs-Fe_3O_4 was introduced into the DDS owing to their enhanced efficacy against Gram-positive and Gram-negative bacteria which is further improved with the synergistic effect of RE. The CQDs were synthesized using a hydrothermal process and have superior antibacterial properties, solubility in water, integration through nanocomposites, whereas Fe_3O_4 provides magnetic and antimicrobial effects and RE reduces cytotoxicity. The structure, the dispersion, and the interaction of the system have been widely determined by the use of SEM, TEM, DLS, zeta potential, FTIR, and XRD. The mechanical testing, porosity and swelling test, and *in vitro* release kinetics ensured that the scaffold had the optimal strength, controlled release and appropriate surface roughness to allow cell proliferation. Biological analysis such as scratch assays and cytotoxicity (MTT) tests using NIH 3T3 cells indicated the high proliferation and migration rate and low toxicity, whereas antibacterial assays indicated strong inhibitory effect against *S. aureus* and *E. coli*. Thus, it can be understood that PVA-CNFs-CQDs-Fe_3O_4-RE DDS is a versatile wound dressing with a long-term antibacterial effect, with good biocompatibility and promotion of wound healing.[97]

5.2 CQDs for other TDDS based applications

Synthesis of an anti-inflammatory nano-drug delivery system using glycyrrhizic acid (GA) functionalized carbon dots (CDs) for methotrexate (MTX) incorporation integrated into MNs, for the targeted treatment of rheumatoid arthritis (RA), was introduced by Chen *et al.* CDs were produced from Poria cocos polysaccharide using a hydrothermal process and functionalized with GA to augment bioactivity and drug loading capacity. Modified CQDs with GA, function as biocompatible, fluorescent carriers for MTX, facilitating effective drug delivery, anti-inflammatory effects, and real-time imaging in the treatment of rheumatoid arthritis. MTX was subsequently incorporated into GA-CDs to create GA-CDs@MTX, which were then combined into dissolvable microneedles for transcutaneous administration. The characterization using TEM, XRD, fluorescence spectroscopy, and zeta potential analysis validated the effective synthesis, structural integrity, and drug-loading efficacy of the nano formulation. *In vitro* studies revealed pH-responsive release of MTX, a notable decrease in inflammatory cytokines (TNF-α, IL-6, IL-1), and efficient cellular uptake as evidenced by fluorescence imaging. *In vivo* findings indicated improved therapeutic results, diminished joint swelling, and absence of skin irritation in rheumatoid arthritis rat models. These data endorse GA-CDs@MTX MNs as a viable approach for the localized, minimally invasive therapy of rheumatoid arthritis as represented in Fig. 5.[98]

Tang *et al.* synthesized nitric oxide-releasing CQDs (CQDs-NO) to enhance the healing of profound partial-thickness burn injuries. The CQDs-NO, synthesized from spermidine at 275 °C, exhibited a particle size of 9.9 nm, elevated zeta potential, photoluminescence, and unique surface chemistry, thereby affirming their structural integrity and usefulness. *In vitro* studies demonstrated prolonged nitric oxide release, negligible cytotoxicity at low concentrations, and augmented migration of human umbilical vein endothelial cells (HUVECs), as well as elevated expression of wound-related proteins (TGF2, HBEGF, LAMB1) all of which were blocked by nitric oxide antagonists, thereby affirming the significance of nitric oxide. Transcriptome analysis indicated that CQDs-NO enhanced the expression of genes associated with angiogenesis, matrix organization, and cell adhesion. *In vivo*, CQDs-NO expedited wound closure, enhanced vascularization, and decreased inflammation in a rat burn model. These findings indicate that CQDs-NO serve as effective NO donors and markedly improve burn wound healing by influencing critical biological pathways and cellular activities.[99]

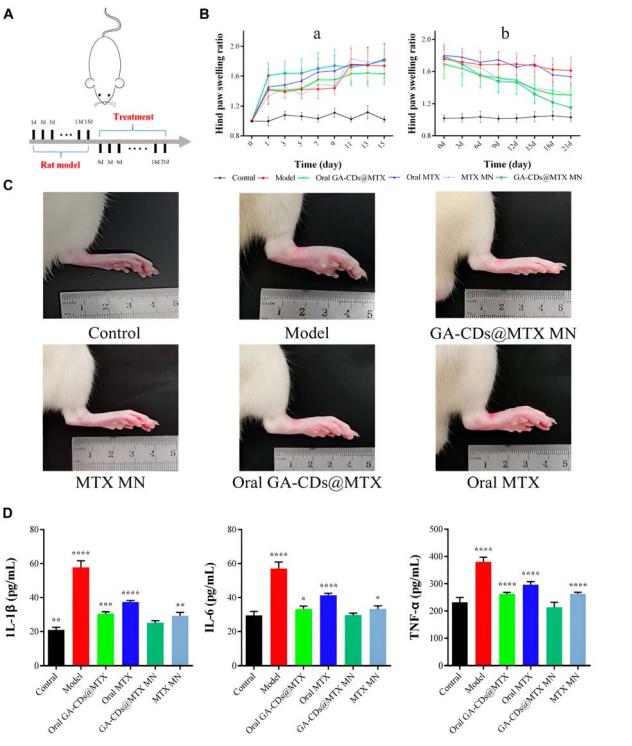

Fig. 5 CQDs incorporated TDDS for treating RA (reproduced from ref. 98 copyright 2023, with permission from *Frontiers*).

Zhang *et al.* fabricated a dual-layer gelatin (GelMA) methacrylate microneedle device that seeks to enhance the healing of diabetic wounds (DWs) through alleviation of oxidative stress and inflammation which are major healing barriers. The selenium-doped CQDs (Se-CQDs) are placed on the outer surface of the microneedles and were prepared using L-selenocystine and analyzed by TEM, atomic force microscopy (AFM), FT-IR, and XPS, confirming the nanoscale size, stability, and functionalities. In the microenvironment of the wound, Se-CQDs can be used as potent antioxidants that can quickly address the excess ROS, which is crucial in ameliorating oxidative stress resulting from chronic hyperglycemia. The inner layer contains astaxanthin (AST) anti-inflammatory and a pro-angiogenic compound that is emitted slowly to achieve M2 macrophage polarization and enhance angiogenesis by cytoskeletal remodeling and the stimulation of pathways related to peroxisomes. Microneedle technology showed sufficient mechanical properties to penetrate the skin, is biocompatible as well as providing a controlled release of the drug within a time frame of 14 days. The effectiveness of the system in accelerating wound closure and improving tissue regeneration was confirmed *in vitro* and *in vivo* including ROS measurements, cell viability measurements, angiogenesis measurements, and diabetic wound models. Se-CQDs are added to the transdermal patch because they have better reactive oxygen species scavenging properties, biocompatibility and the ability to transport drugs on the nanoscale, hence they are best suited to provide immediate oxidative stress relief when applied to the skin. This is a practical way of managing the clinical needs of diabetic wounds through the use of this synergistic and temporally regulated delivery system.[100]

Lv *et al.* fabricated a hyaluronic acid-based microneedle patch embedded with Mn-CQDs (manganese doped CQDs) as a multifunctional nanocarrier to deliver oral squamous cell carcinoma therapy. Mn-CQDs were prepared *via* a one pot solvothermal reaction of ethylenediaminetetraacetic acid manganese disodium salt and *o*-phenylenediamine. Once purified, its encapsulated onto the dissolvable microneedles through sequential casting of Mn-CDs-HA solution in the PVA base in a PDMS mold, as shown in Fig. 6. The comprehensive

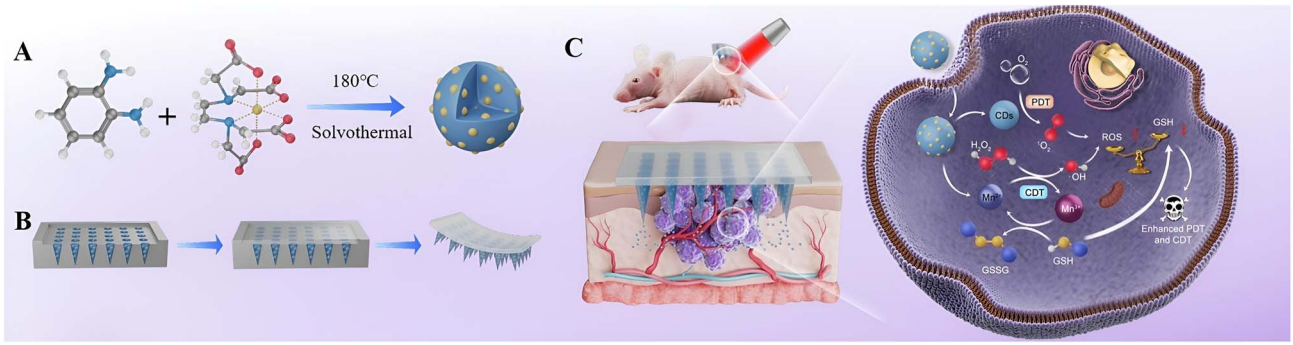

Fig. 6 Schematic overview of the synthesis, delivery, and therapeutic mechanism of carbon dot-based microneedle (MN) systems for carcinoma treatment (reproduced from ref. 101 copyright 2022, with permission from Elsevier).

characterization techniques are TEM, HR-TEM which verifies nanoscale particle size (2.5 nm) and crystallinity, DLS and zeta potential were used to validate the nanoscale hydrodynamic size (7 nm), confirming the nanoscale size and surface chemistry. The FTIR and UV-vis analyses aided in the study of the stability of the system. The drug distribution and mechanical properties for penetration of the system in mucosal tissue was also studied. The effective cellular uptake, strong reactive oxygen species production, depletion of glutathione, and high cytotoxic and apoptotic activities *in vitro* were effectively demonstrated in the biological studies. Thus, the synergistic effect of the photodynamic–chemodynamic cancer therapy was validated for the system.[101]

CQDs play a versatile role in TDDS, owing to their diminutive dimensions and surface modifications, CQDs can efficiently cross the skin barrier, enhancing drug permeability and targeted delivery. Their vast surface area facilitates efficient drug loading, while their surface functionalization allows controlled and sustained drug release. CQDs inherently exhibit antibacterial capabilities, primarily through ROS production, which can compromise bacterial cell membranes which is particularly advantageous for the treatment of infected or chronic wounds. In addition to their antibacterial properties, CQDs demonstrate antioxidant and anti-inflammatory activity that alleviates oxidative stress and inflammation that is typically found in wound sites, as summarized in Table 2. Their superior biocompatibility and low cytotoxicity make them suitable for prolonged skin contact. CQDs are potential delivery agents for therapeutics through biological barriers, such as the blood–brain barrier, but optimization challenges for synthesis, stability, and safety need to be met in order to push clinical applications forward. Moreover, their inherent fluorescence offers a distinct advantage for real-time imaging and drug distribution monitoring, facilitating integrated therapeutic and diagnostic (theragnostic) applications in dermatological treatments.

6 Biocompatibility

Carbon quantum dots are known for their enhanced biocompatibility when compared with traditional semiconductor based quantum dots. The inert carbon core is surface functionalized and passivated to tweak their surface and physicochemical properties.[102] Although CQDs have low cytotoxicity and display good hemocompatibility (hemolysis <5%), cationic surface functionalization, for example with polyethyleneimine, have been found to cause dose dependent toxicity due to various mechanisms such as mitochondrial oxidative stress, membrane depolarization and genotoxic DNA strand breaks, whereas neutral or anionic surfaces usually have no impact.[103,104] Importantly, the biodistribution and clearance routes of CQDs determine their *in vivo* translational safety as they are cleared in the kidney, thus avoiding the chronic hepatotoxicity and inflammatory responses of the reticuloendothelial system (RES) during clearance of bigger (>10 nm) or aggregated particles.[105] CQDs can be made of natural precursors to be exceptionally biocompatible with the cells of the keratinocytes and fibroblasts.[106] In addition to this, their natural fluorescence can be used to track drug penetration through the skin layers in real-time, non-invasively, without using any extra fluorophores, which may prove to be toxic.

7 Challenges and limitations

The skin, being a multilayered tissue, has high resistance to permeability, thus limiting the absorption of therapeutics, especially larger molecules or hydrophilic drugs.[18] Other difficulties faced include skin irritation, sensitization, bacterial or microbial infection and metabolism degradation of the administered therapeutics by the skin enzymes, which can lead to decreased efficacy or safety of therapeutics.[107] Most of the enhancement strategies used are laser ablation, lipid or chemical enhancers, or electroporation, which are potentially toxic and necessitate challenging patient compliance.

Integration of CQDs into TDDS enhances their therapeutic efficacy. CQDs because of their distinctive characteristics improve drug delivery capabilities. Their extensive surface area and functionalization capacity facilitate effective drug loading and regulated release. CQDs possess inherent fluorescence, which facilitates real-time visualization and tracking of drug distribution.[108] Their antioxidant and anti-inflammatory qualities help to manage oxidative stress and inflammation in conditions such as diabetes and neurodegenerative diseases.[109] Furthermore, CQDs can be designed to selectively target certain

Table 2 Comprehensive summary of the role of CQDs in TDDS

Application	Matrix	Drug/CQD	Advantages of nanocarrier – CQDs	References
Wound healing	β-Cyclodextrin and poly *N*-vinyl caprolactam	Lidocaine hydrochloride monohydrate	Real-time monitoring, less cytotoxicity and biocompatible	85
Wound healing	—	Nitrogen doped carbon dots	Real-time monitoring, antimicrobial and antibacterial properties	86
Wound healing	—	Positively charged nitrogen doped carbon quantum dots	Antibacterial properties, less cytotoxic and biocompatible	87
Wound healing	Oxidized dextran and carboxymethyl chitosan	Gentamicin-modified carbon quantum dots	Enhanced collagen deposition and reduced inflammation	88
Wound healing	Chitosan	Gentamicin	Antibacterial and antimicrobial	89
Wound healing	Chitosan and fibroin	Tricalcium phosphate	Antibacterial and tissue regeneration	90
Wound healing	—	Ginger-derived carbon quantum dots	Anti-inflammatory and real-time monitoring	91
Wound healing	Chitosan and polyvinyl alcohol	Turmeric-derived carbon quantum dots	Antibacterial properties and enhanced collagen deposition	92
Wound healing	—	Copper doped carbon quantum dots	Antibacterial, antioxidant, and angiogenic properties	93
Wound healing	—	Porphyrin functionalized CQDs	Antibacterial and real time monitoring	94
Wound healing	Gelatin, chitosan and polycaprolactone	Ag doped CQDs	Antibacterial and faster collagen deposition	95
Wound healing	Cellulose nanofibers	Modified CQDs	Antibacterial and real time monitoring	96
Wound healing	Cellulose nanofibers PVA scaffold	CQDs,Fe_3O_4 NPs and rosemary extract	Antibacterial	97
Rheumatoid arthritis	Glycyrrhizic acid functionalized carbon quantum dots	Methotrexate	Anti-inflammatory and real-time monitoring	98
Burns	—	Nitric oxide releasing carbon quantum dots	Anti-inflammatory and angiogenic	99
Diabetic wound healing	Methacrylate gelatin	Selenium doped carbon quantum dots	Anti-inflammatory, antioxidant and angiogenic	100
Carcinoma therapy	PVA base in PDMS mold	Mn-CQDs	Photodynamic and chemodynamic therapy	101

tissues or cells, enhancing the accuracy of drug delivery and minimizing off-target effects, which is advantageous in cancer therapy. Unification of CQDs and TDDS creates new opportunities for the advancement of non-invasive, multifunctional, and patient-centric therapies of the next generation. As research progresses, CQDs can be customized for personalized medicine by integrating therapeutic delivery with diagnostic functions (theragnostic).[110] Their capability to administer biologics, nucleic acids, or function as biosensors integrated into wearable patches introduces a futuristic aspect to transdermal therapies. Ongoing advancements in materials science and nanotechnology are anticipated to improve these systems, rendering CQD-based TDDS a versatile platform for tackling complicated diseases with increased efficacy, safety, and patient compliance.

CQD-based transcutaneous systems have not yet progressed to human clinical trials despite showing promising results *in vitro* and animal studies. The current phase of research is at a preclinical stage which is mainly the fundamental material characterization and biological evaluation in cell cultures and animal models. There are multiple factors that have hindered the clinical studies of these systems. Firstly, the need for large-scale and long-term preclinical safety and efficacy data is required, cautious regulatory validation, plus financial and logistical factors involved in clinical translation. The majority of studies have worked on developing proof-of-concept, optimization of hydrogels, and evaluation of the *in vivo* wound healing, and research has been mostly performed in rodent model and *in vitro* tests. Therefore, systems are at the initial preclinical stage of development awaiting further validation before they can be advanced clinically.

8 Discussion and future scope

Transcutaneous drug delivery systems are progressively being utilized for the treatment of several ailments beyond wound

healing, such as cancer, diabetes, neurological disorders, and chronic inflammatory problems. This method provides multiple clinical benefits, including consistent medication release, prevention of gastrointestinal degradation, enhanced patient adherence, and decreased dose frequency. In cancer, TDDS facilitate targeted administration of chemotherapeutics, therefore reducing systemic toxicity.[111,112] The addition of CQDs into TDDS for breast cancer enhances drug efficacy and facilitates the advancement of tailored, image-guided therapeutic platforms. This dual functionality facilitates concurrent treatment and monitoring, enhancing illness management and results.[110] In diabetes care, transdermal patches can be engineered for the regulated release of insulin or hypoglycemic drugs.[113] Neurological and psychiatric disorders are being investigated as targets for TDDS, facilitating the non-invasive delivery of medications that typically necessitate invasive or systemic administration methods owing to their ability to cross the blood–brain barrier without any additional ligand added to the DDS.[114,115]

Thus, CQDs are incorporated into TDDS to provide a revolutionary approach to modern medicine. The unique properties of CQDs such as adjustable surface chemistry, fluorescence, and biocompatibility, helps in developing formulation for TDDS of precise, regulated, and monitored drug delivery. They have low toxicity and efficient renal clearance thus decreasing the chances of accumulation after systemic absorption. CQDs have been suggested to be effective nanocarriers in TDD due to their biocompatibility, which enhances the duration of skin contact, patient compliance, and safe increase of drug permeation. With the development of interdisciplinary research, CQD facilitated TDDS has great potential of revolutionizing the process of diagnosis, monitoring and treatment of complex diseases through non-invasive and multipurpose medicines.

9 Conclusions

This review article puts forward CQDs as a new generation of nanocarrier in drug delivery. Unlike traditional nanomaterials, CQDs possess some unique characteristics including tunable fluorescence, high water solubility, high biocompatibility, and low toxicity, which makes them useful in drug delivery and real-time imaging research. Transcutaneous drug delivery is a non-invasive form of drug delivery, unlike other oral and injectable approaches, which bypasses the gastrointestinal tract and the hepatic first-pass metabolism, which enhances drug bioavailability, extends treatment, and increases patient compliance. Despite these advantages, TDDS are faced with significant challenges such as limited drug penetration through the skin barrier, poor solubility of certain therapies, and high dose delivery. Nanoparticles represent a viable alternative due to their small size, surface adjustable properties and excellent skin penetrating properties. Nanoparticles with a diameter of 1–10 nm are the most efficient in passing the stratum corneum and reaching the desired layers of the tissue without causing harm.

Although CQDs have great potential in TDD, various problems exist, including potential toxicity due to impurities in synthesis, low skin permeability in aggregated particles, rapid clearance which reduces the cumulative release of drugs, and difficulties in scaling up to clinical use. In a bid to overcome these difficulties, scientists are striving to enhance synthesis methods to produce purer and safer CQDs, smaller and stable particles to enhance skin permeability, integration of CQDs in delivery systems like nanogels to have sustained release, and scalable and sustainable methods of production.

CQDs are unique in terms of their dual functionality, which is not shared by traditional carriers. Intrinsic antibacterial, antioxidant and anti-inflammatory properties also enable CQDs to combat infections and eradicate oxidative stress and inflammation in wound conditions, which makes CQDs a great choice to heal a wound. Moreover, CQDs can easily be functionalized with various medicines or ligands and this allows the creation of customized and adaptable drug delivery systems that for many diseases.

Author contributions

Veena Venugopal: writing original draft and editing; B. Siva Kumar: supervision, review, and editing; S. Giridhar Reddy: supervision, review, and editing; Sai Manohar Thota: review, and editing.

Conflicts of interest

The authors report that there are no competing interests to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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