



**INTERNATIONAL JOURNAL OF
PHARMACEUTICAL SCIENCES**
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: <https://www.ijpsjournal.com>



Research Article

Silver–Curcumin Hydrogel Systems for Diabetic Wound Healing: Formulation Strategies, Mechanisms, Evaluation and Therapeutic Perspectives

Sachin Yadav*, Dr. Thawkar Sukdeo, Dr. Atul Tripathi

Konkan Gyanpeeth Rahul Dharkar College of Pharmacy and Research Institute, Karjat, Maharashtra, India.

ARTICLE INFO

Published: 14 Oct 2026

Keywords:

Diabetic wound healing,
Silver nanoparticles, Cur-
cumin, Hydrogel, Controlled
drug release, Antibacterial

DOI:

10.5281/zenodo.23360101

ABSTRACT

Diabetic wounds, particularly diabetic foot ulcers, remain among the most burdensome complications of diabetes mellitus because persistent hyperglycaemia, oxidative stress, chronic inflammation, impaired angiogenesis and recurrent infection together stall the normal sequence of repair. Conventional dressings and systemic antibiotics seldom address these overlapping defects at once. Hydrogels are attractive topical carriers because their hydrated three-dimensional networks maintain a moist wound environment, absorb exudate and permit controlled release of loaded agents. Silver, in ionic and nanoparticulate form, provides broad-spectrum antimicrobial and anti-biofilm activity, whereas curcumin, the principal polyphenol of *Curcuma longa*, offers antioxidant, anti-inflammatory, pro-angiogenic and collagen-promoting actions but is limited by poor aqueous solubility and instability. Combining the two within a single hydrogel is therefore a rational multi-target strategy. This review summarises the pathophysiology of impaired diabetic healing, the properties of silver and curcumin relevant to wound care, polymer matrices, formulation and crosslinking strategies, proposed mechanisms of complementary action, and the physicochemical and biological methods used for evaluation. Safety, silver accumulation, regulatory and scale-up challenges are discussed, and future directions such as stimuli-responsive, injectable and sensor-integrated systems are outlined. Silver–curcumin hydrogels show considerable preclinical promise, but standardised testing and well-designed clinical trials are required before clinical translation.

*Corresponding Author: Sachin Yadav

Address: Konkan Gyanpeeth Rahul Dharkar College of Pharmacy and Research Institute, Karjat, Maharashtra, India

Email ✉: ysachinofficial1@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder whose long-term complications place a heavy clinical and economic burden on health systems. Among these, diabetic foot ulceration is one of the most serious. The lifetime risk of a person with diabetes developing a foot ulcer has been estimated at 19–34%, and ulcers frequently recur after apparent healing.¹ A meta-analysis of studies from many regions reported a global prevalence of diabetic foot ulcer of roughly 6% among people with diabetes.² Non-healing ulcers are a major precursor of infection, hospitalisation and lower-limb amputation, and they are associated with reduced quality of life and increased mortality.^{1,3}

Normal cutaneous repair proceeds through overlapping phases of haemostasis, inflammation, proliferation and remodelling, coordinated by platelets, immune cells, keratinocytes, fibroblasts and endothelial cells.^{4,5} In diabetes this orchestrated sequence is disturbed at several levels. Hyperglycaemia drives the accumulation of advanced glycation end-products and excess reactive oxygen species (ROS), inflammation fails to resolve, angiogenesis and neurovascular supply are impaired, proteolytic enzymes degrade the extracellular matrix (ECM) and growth factors, and microbial colonisation, often organised as biofilm, sustains the cycle.^{6–8} Current standard care combines glycaemic control, offloading, debridement, infection management, revascularisation where indicated and moisture-balanced dressings.^{3,9} Yet a considerable proportion of wounds remain unhealed, which reflects the fact that most single-mode interventions address only one of several concurrent defects.¹⁰

Silver has been used in wound care for a long time, and silver ions and silver nanoparticles (AgNPs) retain broad-spectrum antimicrobial activity against bacteria, including strains resistant to common antibiotics.^{11–13} Concerns remain regarding cytotoxicity to host cells, silver accumulation and the potential for bacterial resistance, which make controlled and localised delivery desirable.^{14,15} Curcumin, the principal curcuminoid of *Curcuma longa* L. (turmeric), is a polyphenol with antioxidant, anti-inflammatory and antimicrobial properties and a broad spectrum of reported pharmacological effects.^{16,17} Its benefits for cutaneous repair

have been documented in several animal models, including diabetic rats.^{18,19} However, curcumin is poorly soluble in water, chemically unstable at neutral to alkaline pH, photosensitive and rapidly metabolised, so that its practical use requires formulation support.^{20,21}

Hydrogels are three-dimensional, hydrophilic polymer networks that can hold large amounts of water. They maintain a moist wound environment, absorb exudate, are generally soft and conformable, and can serve as depots for sustained local release of therapeutic agents.^{22–24} A hydrogel is therefore a natural vehicle in which a metal-based antimicrobial and a hydrophobic phytochemical can be combined. The resulting silver–curcumin (Ag–Cur) hydrogel aims to control infection and oxidative inflammation at the same time as supporting the proliferative and remodelling phases of healing.²⁵

Studies on Ag–Cur systems are scattered across materials science, pharmaceuticals and wound biology, and use diverse polymers, preparation routes and test models. The purpose of this review is to bring this information together. It describes the pathophysiology of impaired diabetic healing, the relevant properties of silver and curcumin, the polymer matrices and formulation strategies used to prepare Ag–Cur hydrogels, the proposed mechanisms of action, and the methods used for physicochemical and biological evaluation. It also discusses safety, translational challenges and future therapeutic perspectives.

MATERIALS AND METHODS

This narrative review was prepared by searching PubMed/MEDLINE, Scopus, Web of Science and Google Scholar for English-language publications, using combinations of the terms “diabetic wound”, “diabetic foot ulcer”, “silver nanoparticles”, “silver”, “curcumin”, “hydrogel”, “wound dressing”, “antibacterial”, “drug release” and “nanocomposite”. Original research articles, reviews, standards and guidelines were considered. Priority was given to studies that described the preparation and characterisation of hydrogels containing silver, curcumin or both, and to studies that evaluated them in vitro or in diabetic wound models. Reference lists of key articles were screened manually for further relevant work.



Information was grouped thematically as pathophysiology, active components, polymer matrices, formulation, mechanisms, evaluation and safety. No quantitative meta-analysis was performed because of the heterogeneity of materials, doses and models.

RESULTS

3.1 Pathophysiology of impaired healing in diabetes

Understanding the defects of diabetic wounds is essential for rational design of a multi-component dressing. Table 1 summarises the normal phases of repair and the corresponding abnormalities in diabetes.

Table 1: Phases of Wound Healing and Abnormalities in Diabetes

Phase	Normal events	Abnormalities in diabetic wounds
Haemostasis	Platelet aggregation, fibrin clot, release of PDGF and TGF- β	Altered platelet function and coagulation; microvascular disease limits perfusion ^{7,26}
Inflammation	Neutrophil and macrophage infiltration, clearance of debris and microbes, then resolution	Prolonged neutrophil and M1 macrophage activity, high TNF- α , IL-1 β and IL-6, impaired phagocytosis, delayed resolution ^{6,27}
Proliferation	Angiogenesis, granulation tissue, fibroblast migration, re-epithelialisation	Reduced VEGF signalling and angiogenesis, impaired fibroblast and keratinocyte migration, high MMP activity ^{26,28}
Remodelling	Collagen deposition and cross-linking, ECM maturation, scar formation	Disordered collagen, weak tensile strength, excessive protease degradation of ECM ^{28,29}

Chronic hyperglycaemia increases flux through polyol and hexosamine pathways and promotes mitochondrial superoxide production, which together with advanced glycation end-products activates inflammatory signalling and damages cells.³⁰ The antioxidant transcription factor NRF2 is important for protection against oxidative stress in wounds, and its activity is compromised in diabetic tissue.³¹ Matrix metalloproteinase (MMP) activity is raised in diabetic ulcers relative to acute wounds, with a high MMP-to-inhibitor ratio, so that newly formed matrix and growth factors are degraded.²⁸ Impaired angiogenesis and neuropathy further reduce oxygen and nutrient supply.²⁶

Infection is another critical factor. Chronic wounds are colonised by mixed aerobic and anaerobic flora, and polymicrobial biofilms embedded in an extracellular polymeric matrix show tolerance to antibiotics and host defences.^{32,33} Because microbial burden, oxidative stress, protease excess and poor perfusion interact, a dressing that influences more than one of these factors has a theoretical advantage over single-target approaches.⁸ The wound microenvironment is also relevant to formulation: chronic wound fluid tends to have an alkaline pH, which affects the stability of pH-sensitive actives such as curcumin and the behaviour of pH-responsive polymers.³⁴

3.2 Silver in wound care

3.2.1 Forms of silver and antimicrobial mechanisms

Silver is used as metallic silver, silver salts (for example silver nitrate and silver sulfadiazine), silver complexes and nanoparticles. Antimicrobial activity depends largely on the release of Ag⁺ ions, so that the dissolution rate, particle size, shape, surface coating and local chemistry of the wound all influence efficacy.^{11,12} Several complementary mechanisms have been proposed. Ag⁺ binds to thiol, amino and phosphate groups of proteins and enzymes and thereby inhibits respiratory and other metabolic enzymes. Silver interacts with and perturbs the bacterial cell envelope, causing increased permeability and leakage, and nanoparticles have been observed to accumulate in and damage bacterial membranes.^{35,36} Silver also promotes intracellular ROS generation and can interact with nucleic acids, which interferes with replication.^{37,38} Because several targets are affected simultaneously, the emergence of resistance is considered less likely than with single-target antibiotics, although silver-resistant strains have been reported and stewardship remains necessary.^{12,15}



3.2.2 Effects on host cells and healing

Besides antimicrobial action, AgNPs have been reported to influence healing in animal models. In a thermal injury model, topical AgNPs were associated with faster re-epithelialisation and a modified cytokine profile.³⁹ Other work indicated that AgNPs can influence the differentiation and migration of keratinocytes and fibroblasts, promoting the transformation of fibroblasts to myofibroblasts and thereby wound contraction.⁴⁰ At the same time, dose-dependent cytotoxicity and genotoxicity toward human cells have been described, which sets a limit on the amount of silver that can be safely applied.¹⁴ The clinical evidence for silver-containing dressings is mixed. A Cochrane review found no clear evidence that topical silver prevents wound infection or promotes healing across wound types, which emphasises the need for targeted, well-designed products and trials.⁴¹

3.2.3 Synthesis of silver nanoparticles

Silver nanoparticles are commonly prepared by chemical reduction of silver nitrate using borohydride, citrate or other reducing agents, with stabilisers or capping agents to prevent aggregation.⁴² Physical methods and photochemical routes are also available. “Green” synthesis uses plant extracts, polysaccharides or other biomolecules as both reducing and capping agents, avoiding toxic reagents; this is attractive for biomedical use, although batch-to-batch reproducibility of extract-based syntheses can be difficult to control.^{13,42} Particle size generally ranges from a few nanometres to about 100 nm, and the optical surface plasmon resonance band, typically observed in the 400–450 nm region for spherical AgNPs, is widely used to monitor formation.⁴²

3.3 Curcumin as a wound-healing agent

Curcumin [(1E,6E)-1,7-bis (4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione] has a molar mass of 368.38 g mol⁻¹ and exists in equilibrium between diketo and keto-enol tautomers.¹⁷ The phenolic hydroxyl groups and the conjugated β -diketone system underlie its radical-scavenging ability and its metal-chelating and reducing properties.^{17,43}

In wound models, curcumin has been reported to accelerate closure, enhance granulation tissue formation, increase collagen and hydroxyproline content, and reduce ROS and lipid peroxidation.^{44,45} Curcumin-incorporated collagen films improved dermal wound healing in rats,⁴⁶ and in streptozotocin-induced diabetic rats topical curcumin accelerated closure while modulating antioxidant enzymes and inflammatory mediators.¹⁹ Mechanistically, curcumin inhibits NF- κ B signalling and thereby reduces TNF- α , IL-1 β and IL-6, activates NRF2-dependent antioxidant defences, and has been associated with increased TGF- β 1 and VEGF expression, fibroblast proliferation and angiogenesis.^{16,18,47} Curcumin also has intrinsic antibacterial activity, though it is moderate compared with that of silver.^{17,18}

The principal obstacle to clinical use is physicochemical. Curcumin is practically insoluble in water at acidic and neutral pH, degrades rapidly in neutral to alkaline solution and is sensitive to light, and its systemic bioavailability is poor because of limited absorption and rapid metabolism.^{20,21} Topical application avoids first-pass metabolism, but solubility, stability and skin retention still require formulation strategies.^{48,49} Moreover, curcumin has been classified as a compound that can give false-positive results in assays, owing to its colour, aggregation and reactivity, which is relevant to biological evaluation and is discussed further below.⁴³ Although numerous clinical trials of curcumin for other conditions have been conducted, evidence for topical diabetic wound treatment in humans is limited.^{50,51}

3.4 Hydrogel matrices for diabetic wound dressings

An ideal wound hydrogel is biocompatible, non-adherent, able to absorb exudate while keeping the wound bed moist, permeable to oxygen, mechanically adequate and easily removable. The concept of moist wound healing dates back to the observation that wounds covered by an occlusive layer re-epithelialise faster than dry wounds.⁵² Hydrogels may be derived from natural polymers, synthetic polymers or combinations; their properties are tuned through polymer concentration, crosslink density and chemistry.^{53,54} Table 2 lists polymers commonly used as matrices for silver and curcumin.



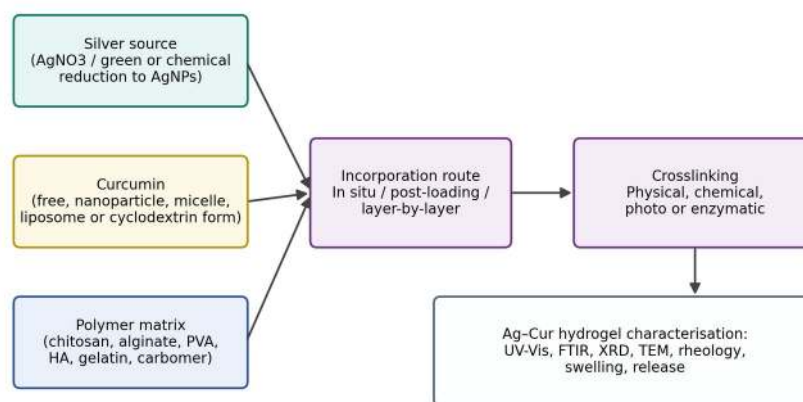
Table 2: Polymer Matrices Used for Silver and Curcumin Hydrogels

Polymer	Key features for wound use	Limitations
Chitosan	Cationic, intrinsic antibacterial and haemostatic activity, promotes granulation; reduces and stabilises AgNPs ⁵⁵	Soluble only in dilute acid; mechanical weakness; variable source and deacetylation degree
Sodium alginate	High exudate absorption, gentle gelation with Ca ²⁺ ions, widely used in commercial dressings ⁵⁶	Low intrinsic bioactivity; ion-dependent stability
Poly(vinyl alcohol) (PVA)	Good mechanical strength and film-forming ability, physical crosslinking by freeze–thaw cycles ⁵⁷	Lacks bioactivity; may need blending for cell adhesion
Gelatin / collagen	Cell-adhesive sequences, biodegradable, supports fibroblast attachment ⁴⁶	Thermally unstable; enzymatic degradation; needs crosslinking
Hyaluronic acid	Hydrating, supports migration and angiogenesis, native to skin ECM ⁵⁸	Rapid enzymatic degradation; cost
Carbomer / cellulose derivatives	Easy to prepare, good spreadability, suited to topical gels ⁵³	Limited biological activity; acidic pre-gel requires neutralisation
Poly(ethylene glycol) and synthetic copolymers	Tunable network, reproducible synthesis, injectable and self-healing designs possible ^{59,60}	Bio-inert; scale-up and regulatory cost for complex designs

Natural polysaccharides such as chitosan and alginate are especially popular for Ag–Cur systems. They are inexpensive, biodegradable and bioactive, and they provide functional groups that can bind or reduce silver and interact with curcumin.^{55,56} Synthetic polymers provide reproducibility and mechanical control, and hybrid networks combine the advantages of both.^{54,61}

3.5 Formulation strategies for silver–curcumin hydrogels

The preparation of an Ag–Cur hydrogel involves selecting the matrix, introducing silver and curcumin in a suitable form, and fixing the network by crosslinking (Fig. 1). The order and method of addition determine particle size, curcumin state, release profile and stability.

**Figure 1: General Workflow for the Preparation of Silver–Curcumin Hydrogels.**

3.5.1 Incorporation of silver

Silver can be introduced in three main ways. In in situ synthesis, AgNO₃ is dissolved within the polymer solution or pre-formed gel and reduced inside the network by the polymer itself (for example chitosan or

polysaccharides with reducing end groups), by an added reductant, by heat or by UV irradiation. This yields well-dispersed nanoparticles stabilised by the matrix and avoids aggregation.^{25,42} In the second approach, pre-formed AgNPs prepared and characterised separately are mixed into the polymer solution,

allowing better control of size and dose but requiring colloidal stability in the pre-gel medium. The third approach employs silver salts or complexes, such as silver sulfadiazine, which release Ag^+ directly. Green routes using plant-derived reductants are widely explored in the literature on silver nanocomposite hydrogels.^{13,25} Because curcumin itself possesses reducing and chelating functionality, it can in principle participate in the reduction and capping of silver ions, so that

in some preparations a single step produces curcumin-capped AgNPs; this can simplify processing but complicates the independent control of the two components.^{17,25}

3.5.2 Incorporation of curcumin

Direct dispersion of crystalline curcumin in an aqueous hydrogel gives poor uniformity and limited bioavailability at the wound surface. Strategies to improve solubilisation and stability are summarised in Table 3.

Table 3: Approaches for Incorporating Curcumin into Hydrogels

Approach	Principle	Consideration
Co-solvent or surfactant solubilisation	Dissolution in ethanol, propylene glycol or micellar surfactant before dispersion in the gel	Simple; solvent or surfactant levels must be compatible with skin and the polymer network
Cyclodextrin inclusion complexes	Host–guest encapsulation increases aqueous solubility and protects from light and hydrolysis ⁴⁹	Requires complexation efficiency optimisation; adds mass to the formulation
Polymeric nanoparticles or micelles	Entrapment in biodegradable particles that are then dispersed in the gel ^{48,49}	Improved stability and sustained release; adds a preparation step
Liposomes, niosomes, nanoemulsions	Lipid-based carriers solubilise the hydrophobic drug and promote skin retention ⁴⁹	Physical stability of vesicles within the gel network
Covalent or ionic conjugation to polymer	Attachment to the polymer backbone gives slow, degradation-dependent release ⁶²	Chemical modification must preserve activity; regulatory complexity

Encapsulation within polymeric or lipid nanocarriers before incorporation into the hydrogel produces a dual-compartment system in which the gel controls the macroscopic behaviour and the nanocarrier controls the curcumin microenvironment, which is a common design in the recent literature.^{49,62}

3.5.3 Crosslinking and gelation

Physical crosslinking relies on reversible interactions, including ionic gelation (alginate with Ca^{2+}), polyelectrolyte complexation, hydrogen bonding and freeze–thaw induced crystallite formation in PVA. These methods avoid potentially toxic crosslinkers and often permit self-healing or injectability but yield weaker networks.^{53,57} Chemical crosslinking using glutaraldehyde, genipin, carbodiimide chemistry or free-radical polymerisation produces stronger networks with controllable swelling and degradation, but residual crosslinker and initiator must be removed or kept below acceptable limits.^{23,53} Photocrosslinking and enzymatic crosslinking offer spatial and temporal control and are compatible with in situ gelation on irregular

wounds. For Ag–Cur hydrogels, the crosslinking method must be compatible with both active components: strong oxidants and high temperatures may degrade curcumin, whereas strong reducing conditions or halide-rich media may alter or precipitate silver species.

3.5.4 Advanced hydrogel designs

Injectable and self-healing hydrogels based on dynamic covalent or supramolecular bonds can conform to deep or irregular ulcers and recover after mechanical disruption.^{59,60} Stimuli-responsive systems are of particular interest for diabetic wounds: pH-responsive gels may release more payload in the alkaline, infected wound environment, and ROS- or enzyme-responsive networks can release curcumin or silver in proportion to oxidative stress or protease activity.^{8,34} Multilayer or bilayer constructs can place a silver-rich antimicrobial layer at the wound contact surface and a curcumin-rich layer for sustained anti-inflammatory delivery. Combination with nanofibrous or foam substrates and the use of microneedle arrays for deeper penetration are



emerging variations, although reports specific to Ag–Cur combinations remain limited.⁶³

3.6 Mechanisms of action of silver–curcumin hydrogels

The rationale for combining silver and curcumin lies in the complementary biological effects of the two agents

and in the supportive role of the hydrogel itself (Fig. 2). The hydrogel provides moisture, exudate management and a physical barrier, and acts as a depot for both actives.^{54,58}

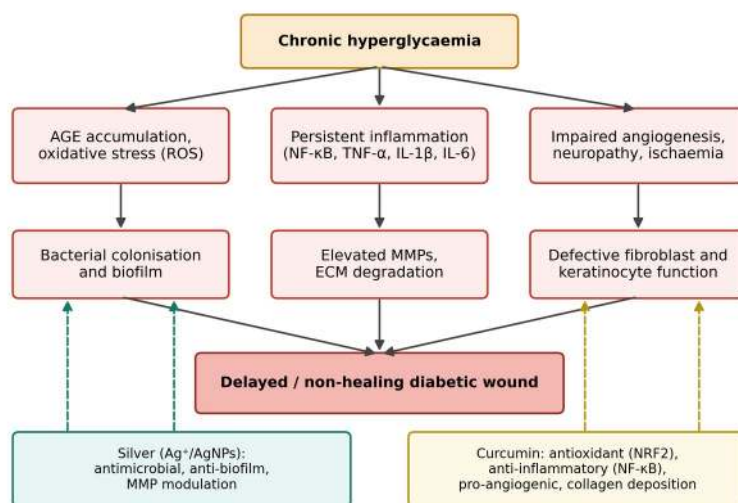


Figure 2: Principal Pathological Mechanisms in the Diabetic Wound and Proposed Points of Action of Silver and Curcumin.

Silver mainly addresses the microbial and biofilm component. Ag⁺ and AgNPs reduce planktonic and surface-associated bacteria, thereby decreasing the continuous stimulus for inflammation and protease production.^{12,37} Curcumin addresses the host response. By suppressing NF-κB signalling and reducing pro-inflammatory cytokines it may allow progression from the inflammatory to the proliferative phase, while its antioxidant properties and activation of NRF2-dependent pathways counter the oxidative stress that damages cells in hyperglycaemic tissue.^{19,31,47} Increased VEGF and TGF-β1 expression, fibroblast proliferation and collagen deposition support granulation and remodelling.^{18,45}

Several types of interaction between the two agents have been proposed. First, curcumin has some antibacterial activity of its own, so that the two agents may contribute additively to microbial control. Second,

by reducing the inflammatory and oxidative load, curcumin may counteract part of the oxidative and cytotoxic stress that silver can induce in host cells, so that a lower silver dose might be sufficient.^{14,19} Third, the polyphenolic structure of curcumin may stabilise AgNPs and modulate the rate of Ag⁺ release.^{17,25} Fourth, the hydrogel network can co-localise and co-release both agents at the wound interface, which helps to achieve simultaneous exposure. Most of these interactions are, however, supported by indirect or in vitro observations, and well-controlled studies that separate additive from truly synergistic effects (for example by isobologram or checkerboard analysis) are uncommon; this point is revisited in the Discussion.

3.7 Physicochemical characterisation

Comprehensive characterisation is necessary to link composition to performance. Table 4 lists the techniques most frequently applied to Ag–Cur hydrogels.

Table 4: Techniques for Physicochemical Characterisation of Silver–Curcumin Hydrogels

Parameter	Technique	Information obtained
Nanoparticle formation	UV–visible spectroscopy	Surface plasmon band of AgNPs (typically 400–450 nm); curcumin absorption in the visible region; changes indicate interaction or degradation ^{17,42}
Size and morphology	TEM, SEM, DLS, zeta potential	Particle size and distribution, shape, dispersion within the network, colloidal stability ⁴²
Crystallinity	XRD	Face-centred cubic silver reflections; amorphous or crystalline state of curcumin ²⁵
Chemical interactions	FTIR, Raman, NMR	Hydrogen bonding, complexation, crosslinking chemistry, drug–polymer compatibility ⁵³
Thermal behaviour	DSC, TGA	Thermal stability, miscibility, water content
Swelling and water handling	Gravimetric swelling, water vapour transmission, moisture retention	Exudate absorption capacity and moist environment maintenance ^{57,58}
Mechanical and rheological	Rheometry, tensile or compression testing, adhesion tests	Viscoelasticity, injectability, strength, self-healing, tack ^{59,60}
Drug and silver release	Franz diffusion cell or dialysis with UV–Vis/HPLC (curcumin) and AAS or ICP-MS (silver)	Release kinetics, Higuchi or Korsmeyer–Peppas modelling ^{64,65}
Degradation and stability	Enzymatic or hydrolytic degradation, accelerated and photostability studies	Shelf-life, curcumin retention, silver speciation ^{21,66}

Release studies deserve particular attention in a dual-component system. Curcumin and silver have different physicochemical properties, so their release profiles differ and should be quantified separately: curcumin by UV–Vis or HPLC under conditions that maintain sink conditions and curcumin stability (for example, medium containing a solubilising agent and protection from light), and silver by atomic absorption spectroscopy or ICP-MS. Release data are often fitted to the Korsmeyer–Peppas model to distinguish Fickian diffusion, anomalous transport and polymer-relaxation-controlled release.^{64,65} Because the aim is to maintain therapeutic concentrations of both agents while avoiding silver overexposure, the quantity of silver released over the dressing wear period should be reported explicitly.

3.8 Biological evaluation

3.8.1 In vitro studies

Antimicrobial activity is generally assessed against Gram-positive and Gram-negative wound pathogens such as *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli* using agar diffusion, minimum inhibitory and bactericidal concentration determinations and time–kill assays; anti-biofilm assays, for example crystal violet or viability staining of

biofilms grown on the material, are more clinically relevant and should be included.^{33,67} Cytocompatibility is evaluated on fibroblasts, keratinocytes or endothelial cells, with extract-based or direct-contact tests following ISO 10993-5.⁶⁸ Metabolic assays such as MTT are widely used,⁶⁹ but the intrinsic colour of curcumin and the optical properties of AgNPs can interfere with colorimetric readouts, so orthogonal methods (for example live/dead staining or ATP-based assays) and appropriate material-only controls are advisable.⁴³ Functional assays include scratch (migration) assays, collagen synthesis, tube formation assays for angiogenesis, and measurement of inflammatory mediators and ROS in stimulated macrophages or in cells cultured under high-glucose conditions to mimic diabetic hyperglycaemia. Haemocompatibility and antioxidant capacity (for example DPPH or ABTS radical scavenging) are commonly reported.

3.8.2 In vivo studies

Diabetic wound efficacy is commonly tested in rodents made diabetic by streptozotocin (STZ), sometimes combined with a high-fat diet, or in genetically diabetic strains, using full-thickness excisional wounds, often stented to limit contraction.⁷⁰ Typical outcome measures are percentage wound closure over time, time to



complete re-epithelialisation, histology of granulation tissue and epidermal thickness, collagen deposition (Masson's trichrome, hydroxyproline), angiogenesis markers such as CD31 and VEGF, inflammatory cytokines, oxidative stress markers and bacterial load in infected wound models. The rat and mouse models

used in studies of curcumin and of AgNPs have reported faster closure and improved histological quality compared with untreated or vehicle controls.^{19,39,48} Table 5 summarises recommended parameters and controls.

Table 5: Recommended Parameters for Biological Evaluation

Level	Parameters	Suggested controls
Antimicrobial	MIC/MBC, zone of inhibition, time–kill, anti-biofilm activity on relevant wound isolates ⁶⁷	Blank hydrogel, silver-only, curcumin-only, and reference antibiotic or commercial silver dressing
Cytocompatibility	Cell viability by two orthogonal assays, live/dead imaging, haemolysis ⁶⁸	Material-only readout controls, negative and positive cytotoxicity controls
Cell function	Scratch closure, collagen synthesis, tube formation, cytokine and ROS levels under high glucose	Normal-glucose and high-glucose conditions
Diabetic animal model	Wound closure kinetics, histology, hydroxyproline, CD31/VEGF, cytokines, bacterial load ⁷⁰	Untreated diabetic, vehicle gel, single-component gels, marketed dressing, non-diabetic reference
Safety	Skin irritation and sensitisation, silver tissue and blood levels, organ histology	Dose-ranging and repeated-application groups

3.9 Safety, stability and regulatory aspects

Silver exposure is the main safety consideration. Although absorption through intact skin is low, absorption through large or chronic wounds can occur, and silver may accumulate in tissues over long-term use; argyria is the best-known consequence of high exposure, and cytotoxic and genotoxic effects have been demonstrated in cell cultures at sufficiently high concentrations.^{11,14,15} Dose-finding studies should therefore aim for the lowest effective silver content and quantify local and systemic silver levels. Curcumin is generally regarded as safe in oral use, but allergic contact dermatitis and staining of skin and dressings can occur.^{50,51}

Stability testing under ICH conditions should evaluate curcumin content, silver speciation and particle aggregation, pH, viscosity, microbial quality and appearance over the intended shelf-life, with protection from light.⁶⁶ Sterilisation is a particular challenge: gamma irradiation and autoclaving may degrade curcumin, alter polymer networks or change AgNP size, so sterilisation methods must be validated for each formulation. From a regulatory perspective, a dressing combining a medicinal component and a nanomaterial may be regulated as a drug, a device or a combination product depending on the jurisdiction and the principal

mode of action, and the nanomaterial status will usually require additional characterisation and toxicological data.^{61,63}

DISCUSSION

4.1 Therapeutic perspectives

The rationale for Ag–Cur hydrogels is conceptually strong. Diabetic wounds are multifactorial and a topical product that simultaneously controls bioburden, modulates inflammation and oxidative stress, and sustains a moist healing environment addresses more than one contributor to chronicity.^{8,10} Preclinical studies with curcumin or AgNPs individually, and with composite hydrogels, consistently report accelerated closure and improved histological parameters in rodent models.^{19,25,39,48} A further potential advantage is dose sparing: if curcumin mitigates oxidative and inflammatory stress, the silver concentration required for antimicrobial efficacy may be kept low, which would improve the benefit–risk balance.

Patient groups that could benefit most include those with infected or critically colonised neuropathic ulcers, patients with recurrent infection or biofilm-associated stalled wounds, and those for whom systemic antibiotics are undesirable because of resistance or renal and



hepatic comorbidity. A hydrogel is also appropriate for dry or sloughy wounds where autolytic debridement and hydration are needed. For ischaemic ulcers, however, topical therapy cannot replace revascularisation, and Ag–Cur hydrogels should be viewed as adjuncts to, not substitutes for, standard care including offloading, debridement and glycaemic control.^{3,9}

4.2 Critical appraisal of the current evidence

Several limitations temper enthusiasm. First, much of the evidence arises from small, short-term studies in rodent models, which differ from human diabetic ulcers in the extent of skin contraction, perfusion, neuropathy and chronicity.⁷⁰ Second, formulations vary so widely

in polymer, silver form, curcumin form and dose that cross-study comparison is difficult, and many papers lack the single-component and commercial-dressing controls that are needed to demonstrate added value. Third, true synergy is rarely tested formally. Fourth, curcumin is a known source of assay interference and has questionable chemical stability, so apparent bioactivity in vitro may not reflect the active species in the wound.^{21,43} Fifth, reporting of silver release, silver tissue levels and long-term safety is inconsistent. Finally, the Cochrane evidence on silver dressings indicates that clinical benefit cannot be assumed from antimicrobial potency alone.⁴¹

4.3 Challenges and possible solutions

Table 6: Key Challenges and Possible Solutions

Challenge	Consequence	Possible approach
Curcumin instability and low solubility	Loss of activity during storage and use	Nanocarrier or cyclodextrin encapsulation, light-protective packaging, pH control ^{21,49}
Silver cytotoxicity and accumulation	Delayed healing, systemic exposure	Low-dose, controlled-release designs; quantification of silver release and tissue levels ^{14,15}
Batch variability of green synthesis	Poor reproducibility	Standardised extracts or defined reductants; process analytical controls ⁴²
Assay interference	Misleading in vitro data	Orthogonal assays; material-only controls ⁴³
Limited relevance of animal models	Poor clinical translation	Infected and ischaemic models, larger-animal or ex vivo human skin models, biofilm models ^{33,70}
Sterilisation and scale-up	Degradation of actives, cost	Validated low-damage sterilisation; aseptic processing; quality-by-design ^{61,66}
Regulatory classification	Prolonged development	Early engagement with regulators; defined primary mode of action ⁶³

4.4 Future directions

Future work should move toward rationally designed, well-characterised systems tested against appropriate controls. Stimuli-responsive hydrogels that release silver in response to infection-associated pH or enzymes, and curcumin in response to ROS, would match drug delivery to wound state.^{8,34} Integration of sensors for pH, temperature or glucose could enable smart dressings that monitor healing and trigger release. Alternatives to AgNPs, such as silver–polymer complexes, bimetallic systems or co-delivery with other natural antimicrobials, may widen the therapeutic window. More robust preclinical models, including infected, ischaemic and biofilm-bearing wounds, should be combined with transparent reporting of formulation and release data. Finally, adequately powered

randomised controlled trials in patients with diabetic foot ulcers, with standardised endpoints such as complete wound closure at 12 weeks, infection rate and adverse events, are required before clinical value can be established.^{3,9}

CONCLUSION

Silver–curcumin hydrogels combine antimicrobial, anti-inflammatory, antioxidant and pro-regenerative actions in a moist, controlled-release dressing, and thus address several of the interacting defects that impede diabetic wound healing. Formulation advances, including in situ and green synthesis of silver nanoparticles, nanocarrier-assisted curcumin loading and responsive or injectable networks, have improved the feasibility of such systems. Preclinical results are



encouraging, but they are limited by heterogeneous designs, inconsistent controls, inadequate assessment of synergy and silver safety, and the absence of clinical data. Standardised characterisation and evaluation, together with carefully designed clinical trials, will determine whether these hydrogels can progress from promising laboratory formulations to effective therapies for patients with diabetic foot ulcers.

ACKNOWLEDGMENT

The authors are thankful to the management and the Principal of Konkan Gyanpeeth Rahul Dharkar College of Pharmacy and Research Institute, Karjat, for providing library and database facilities.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest related to the publication of this manuscript.

AUTHOR CONTRIBUTIONS

SachinYadav: conceptualisation, literature search, data compilation and drafting of the manuscript; Dr.B.S.T. and Dr.A.T.: guidance, supervision and critical revision of the manuscript. All authors read and approved the final manuscript.

REFERENCES

1. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. *N Engl J Med*. 2017;376:2367-75.
2. Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis. *Ann Med*. 2017;49:106-16.
3. Armstrong DG, Tan TW, Boulton AJM, Bus SA. Diabetic foot ulcers: a review. *JAMA*. 2023;330:62-75.
4. Gurtner GC, Werner S, Barrandon Y, Longaker MT. Wound repair and regeneration. *Nature*. 2008;453:314-21.
5. Eming SA, Martin P, Tomic-Canic M. Wound repair and regeneration: mechanisms, signaling, and translation. *Sci Transl Med*. 2014;6:265sr6.
6. Brem H, Tomic-Canic M. Cellular and molecular basis of wound healing in diabetes. *J Clin Invest*. 2007;117:1219-22.
7. Falanga V. Wound healing and its impairment in the diabetic foot. *Lancet*. 2005;366:1736-43.
8. Patel S, Srivastava S, Singh MR, Singh D. Mechanistic insight into diabetic wounds: pathogenesis, molecular targets and treatment strategies to pace wound healing. *Biomed Pharmacother*. 2019;112:108615.
9. Lipsky BA, Senneville E, Abbas ZG, Aragon-Sanchez J, Diggle M, Embil JM, et al. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020;36 (Suppl 1):e3280.
10. Frykberg RG, Banks J. Challenges in the treatment of chronic wounds. *Adv Wound Care*. 2015;4:560-82.
11. Lansdown AB. Silver in health care: antimicrobial effects and safety in use. *Curr Probl Dermatol*. 2006;33:17-34.
12. Chernousova S, Eppler M. Silver as antibacterial agent: ion, nanoparticle, and metal. *Angew Chem Int Ed Engl*. 2013;52:1636-53.
13. Rai M, Yadav A, Gade A. Silver nanoparticles as a new generation of antimicrobials. *Biotechnol Adv*. 2009;27:76-83.
14. AshaRani PV, Low Kah Mun G, Hande MP, Valiyaveetil S. Cytotoxicity and genotoxicity of silver nanoparticles in human cells. *ACS Nano*. 2009;3:279-90.
15. Vimbela GV, Ngo SM, Frazee C, Yang L, Stout DA. Antibacterial properties and toxicity from metallic nanomaterials. *Int J Nanomedicine*. 2017;12:3941-65.
16. Aggarwal BB, Sung B. Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets. *Trends Pharmacol Sci*. 2009;30:85-94.
17. Priyadarsini KI. The chemistry of curcumin: from extraction to therapeutic agent. *Molecules*. 2014;19:20091-112.



18. Akbik D, Ghadiri M, Chrzanowski W, Rohanizadeh R. Curcumin as a wound healing agent. *Life Sci.* 2014;116:1-7.
19. Kant V, Gopal A, Pathak NN, Kumar P, Tandan SK, Kumar D. Antioxidant and anti-inflammatory potential of curcumin accelerated the cutaneous wound healing in streptozotocin-induced diabetic rats. *Int Immunopharmacol.* 2014;20:322-30.
20. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. *Mol Pharm.* 2007;4:807-18.
21. Wang YJ, Pan MH, Cheng AL, Lin LI, Ho YS, Hsieh CY, et al. Stability of curcumin in buffer solutions and characterization of its degradation products. *J Pharm Biomed Anal.* 1997;15:1867-76.
22. Drury JL, Mooney DJ. Hydrogels for tissue engineering: scaffold design variables and applications. *Biomaterials.* 2003;24:4337-51.
23. Hoffman AS. Hydrogels for biomedical applications. *Adv Drug Deliv Rev.* 2012;64 (Suppl):18-23.
24. Peppas NA, Hilt JZ, Khademhosseini A, Langer R. Hydrogels in biology and medicine: from molecular principles to bionanotechnology. *Adv Mater.* 2006;18:1345-60.
25. Varaprasad K, Mohan YM, Vimala K, Mohana Raju K. Synthesis and characterization of hydrogel-silver nanoparticle-curcumin composites for wound dressing and antibacterial application. *J Appl Polym Sci.* 2011;121:784-96.
26. Okonkwo UA, DiPietro LA. Diabetes and wound angiogenesis. *Int J Mol Sci.* 2017;18:1419.
27. Wilkinson HN, Hardman MJ. Wound healing: cellular mechanisms and pathological outcomes. *Open Biol.* 2020;10:200223.
28. Lobmann R, Ambrosch A, Schultz G, Waldmann K, Schiweck S, Lehnert H. Expression of matrix-metalloproteinases and their inhibitors in the wounds of diabetic and non-diabetic patients. *Diabetologia.* 2002;45:1011-6.
29. Rodrigues M, Kosaric N, Bonham CA, Gurtner GC. Wound healing: a cellular perspective. *Physiol Rev.* 2019;99:665-706.
30. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature.* 2001;414:813-20.
31. Long M, Rojo de la Vega M, Wen Q, Bharara M, Jiang T, Zhang R, et al. An essential role of NRF2 in diabetic wound healing. *Diabetes.* 2016;65:780-93.
32. Bowler PG, Duerden BI, Armstrong DG. Wound microbiology and associated approaches to wound management. *Clin Microbiol Rev.* 2001;14:244-69.
33. James GA, Swogger E, Wolcott R, Pulcini E, Secor P, Sestrich J, et al. Biofilms in chronic wounds. *Wound Repair Regen.* 2008;16:37-44.
34. Schneider LA, Korber A, Grabbe S, Dissemmond J. Influence of pH on wound-healing: a new perspective for wound-therapy? *Arch Dermatol Res.* 2007;298:413-20.
35. Sondi I, Salopek-Sondi B. Silver nanoparticles as antimicrobial agent: a case study on *E. coli* as a model for Gram-negative bacteria. *J Colloid Interface Sci.* 2004;275:177-82.
36. Morones JR, Elechiguerra JL, Camacho A, Holt K, Kouri JB, Ramirez JT, et al. The bactericidal effect of silver nanoparticles. *Nanotechnology.* 2005;16:2346-53.
37. Dakal TC, Kumar A, Majumdar RS, Yadav V. Mechanistic basis of antimicrobial actions of silver nanoparticles. *Front Microbiol.* 2016;7:1831.
38. Prabhu S, Poullose EK. Silver nanoparticles: mechanism of antimicrobial action, synthesis, medical applications, and toxicity effects. *Int Nano Lett.* 2012;2:32.
39. Tian J, Wong KK, Ho CM, Lok CN, Yu WY, Che CM, et al. Topical delivery of silver nanoparticles promotes wound healing. *ChemMedChem.* 2007;2:129-36.
40. Liu X, Lee PY, Ho CM, Lui VC, Chen Y, Che CM, et al. Silver nanoparticles mediate differential responses in keratinocytes and fibroblasts during skin wound healing. *ChemMedChem.* 2010;5:468-75.
41. Storm-Versloot MN, Vos CG, Ubbink DT, Vermeulen H. Topical silver for preventing wound



- infection. *Cochrane Database Syst Rev.* 2010; (3):CD006478.
42. Lee SH, Jun BH. Silver nanoparticles: synthesis and application for nanomedicine. *Int J Mol Sci.* 2019;20:865.
43. Nelson KM, Dahlin JL, Bisson J, Graham J, Pauli GF, Walters MA. The essential medicinal chemistry of curcumin. *J Med Chem.* 2017;60:1620-37.
44. Sidhu GS, Singh AK, Thaloor D, Banaudha KK, Patnaik GK, Srimal RC, et al. Enhancement of wound healing by curcumin in animals. *Wound Repair Regen.* 1998;6:167-77.
45. Panchatcharam M, Miriyala S, Gayathri VS, Suguna L. Curcumin improves wound healing by modulating collagen and decreasing reactive oxygen species. *Mol Cell Biochem.* 2006;290:87-96.
46. Gopinath D, Ahmed MR, Gomathi K, Chitra K, Sehgal PK, Jayakumar R. Dermal wound healing processes with curcumin incorporated collagen films. *Biomaterials.* 2004;25:1911-7.
47. Kunnumakkara AB, Bordoloi D, Padmavathi G, Monisha J, Roy NK, Prasad S, et al. Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases. *Br J Pharmacol.* 2017;174:1325-48.
48. Mohanty C, Das M, Sahoo SK. Sustained wound healing activity of curcumin loaded oleic acid based polymeric bandage in a rat model. *Mol Pharm.* 2012;9:2801-11.
49. Yallapu MM, Jaggi M, Chauhan SC. Curcumin nanoformulations: a future nanomedicine for cancer. *Drug Discov Today.* 2012;17:71-80.
50. Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: lessons learned from clinical trials. *AAPS J.* 2013;15:195-218.
51. Hewlings SJ, Kalman DS. Curcumin: a review of its effects on human health. *Foods.* 2017;6:92.
52. Winter GD. Formation of the scab and the rate of epithelization of superficial wounds in the skin of the young domestic pig. *Nature.* 1962;193:293-4.
53. Ahmed EM. Hydrogel: preparation, characterization, and applications: a review. *J Adv Res.* 2015;6:105-21.
54. Gupta A, Kowalczyk M, Heaselgrave W, Britland ST, Martin C, Radecka I. The production and application of hydrogels for wound management: a review. *Eur Polym J.* 2019;111:134-51.
55. Muzzarelli RA. Chitins and chitosans for the repair of wounded skin, nerve, cartilage and bone. *Carbohydr Polym.* 2009;76:167-82.
56. Varaprasad K, Jayaramudu T, Kanikireddy V, Toro C, Sadiku ER. Alginate-based composite materials for wound dressing application: a mini review. *Carbohydr Polym.* 2020;236:116025.
57. Kamoun EA, Kenawy ER, Chen X. A review on polymeric hydrogel membranes for wound dressing applications: PVA-based hydrogel dressings. *J Adv Res.* 2017;8:217-33.
58. Boateng JS, Matthews KH, Stevens HN, Eccleston GM. Wound healing dressings and drug delivery systems: a review. *J Pharm Sci.* 2008;97:2892-923.
59. Zhao X, Wu H, Guo B, Dong R, Qiu Y, Ma PX. Antibacterial anti-oxidant electroactive injectable hydrogel as self-healing wound dressing with hemostasis and adhesiveness for cutaneous wound healing. *Biomaterials.* 2017;122:34-47.
60. Qu J, Zhao X, Liang Y, Zhang T, Ma PX, Guo B. Antibacterial adhesive injectable hydrogels with rapid self-healing, extensibility and compressibility as wound dressing for joint skin wound healing. *Biomaterials.* 2018;183:185-99.
61. Caló E, Khutoryanskiy VV. Biomedical applications of hydrogels: a review of patents and commercial products. *Eur Polym J.* 2015;65:252-67.
62. Alven S, Nqoro X, Aderibigbe BA. Polymer-based materials loaded with curcumin for wound healing applications. *Polymers (Basel).* 2020;12:2286.
63. Hamdan S, Pastar I, Drakulich S, Dikici E, Tomic-Canic M, Deo S, et al. Nanotechnology-driven therapeutic interventions in wound healing: potential uses and applications. *ACS Cent Sci.* 2017;3:163-75.
64. Ritger PL, Peppas NA. A simple equation for description of solute release II. Fickian and

anomalous release from swellable devices. *J Control Release*. 1987;5:37-42.

65. Siepmann J, Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). *Adv Drug Deliv Rev*. 2001;48:139-57.
66. International Council for Harmonisation. ICH Q1A (R2): Stability testing of new drug substances and products. Geneva: ICH; 2003.
67. Balouiri M, Sadiki M, Ibensouda SK. Methods for in vitro evaluating antimicrobial activity: a review. *J Pharm Anal*. 2016;6:71-9.
68. International Organization for Standardization. ISO 10993-5:2009. Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity. Geneva: ISO; 2009.
69. Mosmann T. Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. *J Immunol Methods*. 1983;65:55-63.
70. Furman BL. Streptozotocin-induced diabetic models in mice and rats. *Curr Protoc Pharmacol*. 2015;70:5.47.1-5.47.20.

HOW TO CITE: Sachin Yadav, Dr. Thawkar Sukdeo, Dr. Atul Tripathi, Silver–Curcumin Hydrogel Systems for Diabetic Wound Healing: Formulation Strategies, Mechanisms, Evaluation and Therapeutic Perspectives, *Int. J. of Pharm. Sci.*, 2026, Vol 4, Issue 10, 2091-2104. <https://doi.org/10.5281/zenodo.23360101>

