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DEVELOPMENT AND EVALUATION OF A MET FOR MIN LOADED pH-RESPONSIVE IN-SITU GELLING SPRAY FOR ENHANCED DIABETIC WOUND HEALING

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1. ABSTRACT - *Diabetic wounds are chronic wounds in which normal repair is disrupted by a complex microenvironment involving persistent inflammation, oxidative stress, impaired angiogenesis, abnormal extracellular-matrix remodelling, infection risk and altered cellular responses. Conventional dressings mainly provide protection and fluid management and may not actively respond to changing wound conditions. Stimuli-responsive hydrogels have therefore emerged as an advanced wound-delivery platform because their swelling, permeability, degradation or mechanical behaviour can change in response to wound-associated signals such as pH, glucose, reactive oxygen species or enzymes [1–4]. Metformin is established as an antidiabetic medicine, but topical metformin has also been investigated as a potential wound-healing intervention. A 2025 systematic review identified 26 studies and reported encouraging preclinical findings involving wound closure, collagen deposition, angiogenic markers, inflammatory signalling and autophagy; however, it also emphasized that clinical evidence remains limited and that appropriate human trials are required [5]. Experimental work has reported that topical metformin can increase collagen-I/III expression and reduce markers associated with apoptosis in diabetic wound models [6]. The present review proposes a sprayable pH-responsive in-situ gel as a local delivery platform. The formulation would be applied as a relatively low-viscosity liquid and then undergo a physicochemical change at the wound surface, increasing local viscosity and residence. This concept combines the potential biological activity of topical metformin with the formulation advantages of responsive hydrogels. A related published study demonstrated a sprayable thermosensitive hydrogel containing zinc-modified metformin, supporting the feasibility of sprayable metformin containing hydrogel systems, although that system was thermosensitive rather than specifically pH-responsive [7].*

Keywords: Metformin; diabetic wound; topical drug delivery; pH-responsive polymer; insitu gel; sprayable hydrogel; smart wound dressing; controlled release.

2. INTRODUCTION

Wound healing is a coordinated biological process involving haemostasis, inflammation, proliferation and tissue remodelling. The process depends on communication between keratinocytes, fibroblasts, endothelial cells, immune cells and extracellular-matrix components. In diabetes, this sequence can become prolonged or dysregulated, producing wounds that remain open for extended periods and are vulnerable to infection and recurrent tissue damage [8–10]. The diabetic wound microenvironment is not static. It may show hyperglycaemia, excessive reactive oxygen species, persistent inflammatory signalling, hypoxia or poor vascularisation, elevated matrix-metalloproteinase activity, altered pH and bacterial colonisation. These abnormalities create a therapeutic challenge because a single passive dressing may not address all stages of the healing process [2–4]. Modern wound delivery research therefore increasingly focuses on biomaterials that can maintain hydration, protect tissue, carry therapeutic molecules and respond to local environmental conditions. Hydrogels are particularly useful because their water-rich three-dimensional networks can provide a moist environment and can be engineered for drug loading and controlled release [2–4]. A pH-responsive in-situ gelling spray is an attractive research concept because it attempts to combine the convenience of spraying with the retention characteristics of a gel. Instead of preparing a preformed sheet or manually spreading a viscous gel, the formulation can be delivered over an irregular wound surface and then undergo a trigger-dependent change after application. The exact trigger conditions and polymer behaviour must, however, be demonstrated experimentally for the selected formulation.

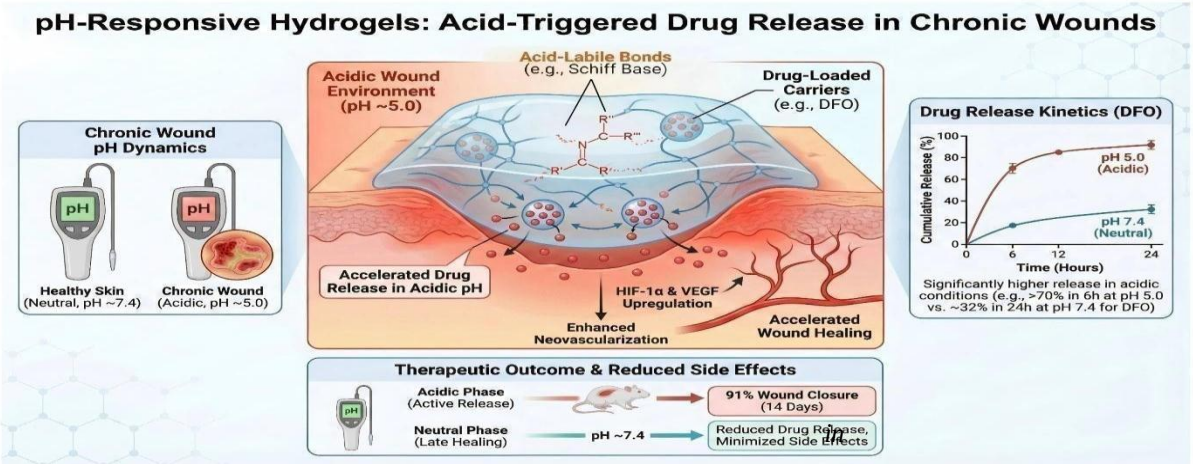

Figure 1. pH - Responsive Hydrogels: Acid -Triggered Drug Release Chronic Wounds.

3. SCOPE AND REVIEW APPROACH

This report is a narrative literature review and formulation-development framework. It integrates published literature on topical metformin, diabetic wound biology, responsive hydrogels and sprayable wound-delivery systems. Particular attention is given to publications indexed in PubMed and to peerreviewed review articles and experimental studies identified during the literature search. The report addresses:

- Biological basis of delayed diabetic wound healing;
- Potential wound-related effects of topical metformin;
- Principles of hydrogel and in-situ gel drug delivery;
- pH-responsive polymer behaviour;
- Proposed spray formulation components and development workflow;
- Pharmaceutical evaluation and quality attributes;
- Limitations, translational barriers and future research needs.

The report does not claim that the proposed formulation is clinically proven. The literature indicates promise, particularly at preclinical level, while human evidence for topical metformin remains limited. [5]

4. DIABETIC WOUND HEALING

Diabetic wounds are chronic wounds associated with diabetes and frequently involve the lower extremities. Their persistence results from multiple interacting abnormalities rather than from a single defect. Hyperglycaemia can influence immune-cell function, vascular biology, oxidative balance and extracellular-matrix turnover. Neuropathy and vascular insufficiency may further increase trauma and reduce tissue repair capacity. Reviews of responsive hydrogels describe the diabetic wound as a microenvironment with high glucose, inflammation, oxidative stress, hypoxia, bacterial burden and variable pH. These characteristics have become important design targets for smart wound dressings [2–4]

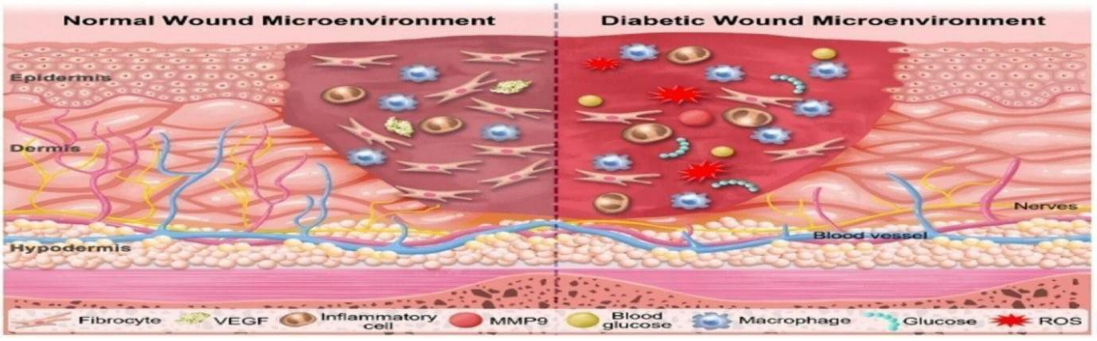

Figure 2: A comparison of the normal and diabetic wound microenvironment.

From a formulation-development perspective, this complexity suggests that the delivery system should be evaluated not only for drug release but also for local retention, hydration, compatibility, mechanical behaviour and microbiological quality.

5. SKIN AND SKIN PH

Skin is the largest organ of the human body and acts as a protective barrier against microorganisms, chemicals, and environmental damage. It consists of three main layers: the epidermis, dermis, and hypodermis.

Skin pH refers to the acidity or alkalinity of the skin surface. Healthy skin generally has an acidic pH of approximately 4.5 5.5, which helps maintain the skin barrier and normal microbial balance.

Wound pH can vary depending on the stage of healing and wound condition. Chronic wounds often have a neutral-to-alkaline environment. These pH changes are important in developing pH-responsive in-situ gelling sprays, which may form a gel under suitable conditions and provide localized drug delivery for wound healing.

In diabetic wound-healing research, understanding skin and wound pH helps researchers design suitable formulations and evaluate drug release, biocompatibility, and healing potential.

6. NORMAL WOUND-HEALING PHASES

- **Haemostasis-**Immediately after injury, vasoconstriction and platelet activation help limit blood loss. A fibrin-rich clot provides a temporary matrix for subsequent cellular migration.
- **In*f*lammation-**Neutrophils and macrophages participate in removal of debris and microorganisms. Controlled inflammation is necessary; excessive or prolonged inflammation can interfere with progression to repair.
- **Proliferation-**Fibroblast activity, extracellular-matrix deposition, angiogenesis, granulation tissue formation and reepithelialisation contribute to restoration of tissue structure.
- **Remodelling-**Collagen is reorganised and tissue strength gradually increases. The balance between matrix synthesis and degradation is important for scar maturation [8 10].

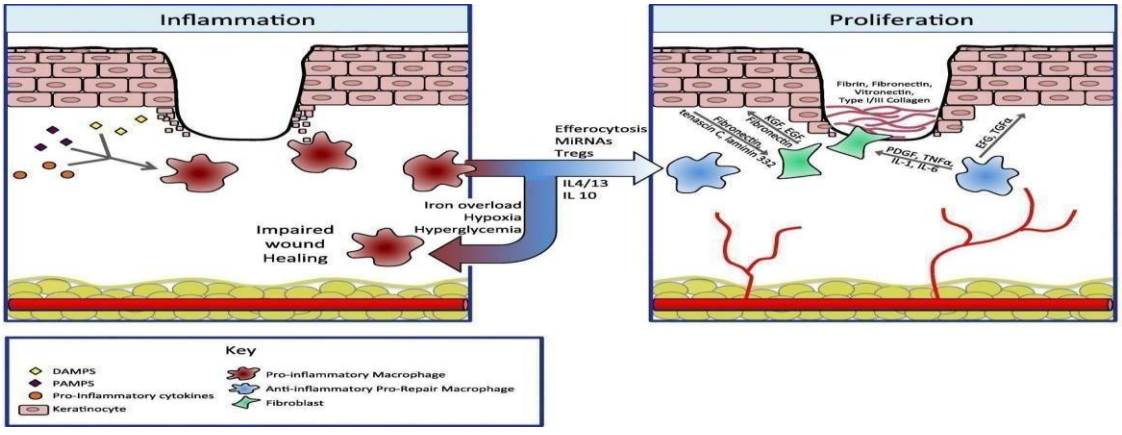

Figure 3: Phases of wound healing

7. PATHOPHYSIOLOGY OF DIABETIC WOUNDS

- **Hyperglycaemia:** Persistently elevated glucose can alter cellular signalling and vascular function and contribute to oxidative stress and impaired immune responses. These effects can delay progression through the normal healing sequence [2 4].
- **Chronic in*f*lammation:** A diabetic wound may remain in a prolonged inflammatory state. Excessive inflammatory mediators and dysregulated immune-cell activity can damage newly forming tissue and prevent efficient transition toward proliferation and remodelling.
- **Oxidative stress:** Reactive oxygen species participate in normal signalling at controlled levels, but excessive ROS can damage lipids, proteins and nucleic acids. Responsive biomaterials are being designed

to counter or exploit this abnormal redox environment [3,4].

- **Impaired angiogenesis and hypoxia:** Adequate blood supply is required for oxygen and nutrient delivery. Impaired vascular responses can contribute to persistent hypoxia and reduced tissue repair.
- **Extracellular-matrix imbalance:** Collagen deposition and remodelling are important for wound closure and strength. Experimental topical metformin work has reported increased collagen-I and collagenIII expression in diabetic wound models [6].
- **Infection and bio*f*ilm formation:** Chronic wounds are susceptible to microbial colonisation and biofilm formation. Infection can further increase inflammation and delay repair. A wound-delivery platform therefore needs adequate microbiological quality and should not create a favourable environment for contamination

8. METFORMIN: PHARMACOLOGICAL BACKGROUND

Metformin hydrochloride is a biguanide antidiabetic drug widely used in the management of type 2 diabetes. Its established clinical role is systemic glucose-lowering therapy. The wound healing literature has generated interest in whether metformin may also exert local biological effects when applied directly to damaged tissue. The mechanisms proposed for wound-related activity include effects on cellular metabolism, inflammatory signalling, oxidative stress, autophagy, apoptosis and extracellular-matrix processes. Because these mechanisms are context-dependent, they should be regarded as biological hypotheses supported to varying degrees by experimental studies rather than as a single confirmed mechanism for clinical wound healing. A diabetic woundmodel study reported that topical metformin increased collagen-I/III expression and decreased p53/c-jun levels and apoptosis-related measures, with improvement in wound repair [6]. Another study developed metformin hydrochloride topical hydrogels and characterised drug content, pH, homogeneity, viscosity, spreadability and invitro release, demonstrating the feasibility of investigating metformin in a topical hydrogel dosage form [11].

Study / Source	System / Focus	Main relevance to present topic
Maghsoodloo et al., 2025 [5]	Systematic review, 26 studies	Summarises topical metformin evidence; highlights promising preclinical results and limited.
Tombulturk et al., 2024 [6]	Diabetic wound model	Reports effects on collagen I/III expression, apoptosis related markers and wound repair.
Liu et al., 2022/2023 [7]	Sprayable thermosensitive Znmetformin hydrogel.	Provides a directly relevant precedent for a sprayable metformincontaining hydrogel.
Tawfeek et al., 2020 [11]	Topical metformin hydrogel	Demonstrates formulation and evaluation of metformin hydrogel; includes drug content.

9. EVIDENCE FOR TOPICAL METFORMIN

The 2025 systematic review by Maghsoodloo et al. evaluated 26 studies of topical metformin and concluded that the preclinical literature contains encouraging findings, including increased wound closure and collagen deposition, higher pro-angiogenic markers, reduced proinflammatory cytokines and induction of autophagy signalling. Importantly, the review also noted that clinical studies are limited and that properly designed human studies are required to determine safety, efficacy and the most suitable delivery modality [5]. The evidence therefore supports the scientific rationale for further formulation research but does not establish a clinically proven topical metformin treatment for diabetic wounds. This distinction is essential in an academic project: formulation development and preclinical evidence should be described separately from clinical efficacy.

10. HYDROGELS IN WOUND MANAGEMENT

Hydrogels are three-dimensional polymeric networks capable of retaining large quantities of water. Their hydrated structure can provide a moist interface, and their composition can be adjusted to control swelling, mechanical properties, adhesion and drug release. Reviews describe hydrogels as promising wound-dressing materials because of

their water content, biocompatibility, drug-carrying capacity and ability to incorporate environmental responsiveness [2].

Types of hydrogel approaches

Natural polymer hydrogels based on materials such as chitosan, alginate, hyaluronic acid or other polysaccharides; Synthetic polymer hydrogels designed for controlled mechanical and release properties;

Composite or hybrid hydrogels combining more than one polymer or therapeutic function; Stimuliresponsive hydrogels that alter swelling, permeability, degradation or mechanical behaviour in response to environmental signals.

Why an in-situ gel can be useful?

A preformed gel may be difficult to distribute evenly over a deep, irregular or difficult-to reach wound. An insitu gel can be administered in a lower-viscosity state and then form a gel after application. This can improve surface coverage and potentially reduce immediate wash off. However, gelation must be sufficiently rapid to provide retention while remaining slow enough to permit reproducible application.

11. STIMULI-RESPONSIVE HYDROGELS

Stimuli-responsive or 'smart' hydrogels are designed to change their physicochemical properties after exposure to a particular stimulus. Reviews of diabetic wound systems describe responsiveness to temperature, pH, glucose, ROS, enzymes and combinations of these triggers. [2]

Stimulus	Typical formulation response	Potential relevance
pH	Ionisation, swelling, contraction or degradation	Can exploit wound pH differences to alter local release or gel properties
Temperature	Sol-gel transition or network change	Useful for thermosensitive sprayable systems.
Glucose	Glucose-dependent chemical or enzymatic response	May allow diabetes-associated glucose sensing.
ROS	ROS-scavenging or ROS-triggered bond cleavage	May address oxidative stress or trigger release.
Enzyme	Enzyme-cleavable linkers degradation	Can respond to wound-associated protease activity
Multistimulus	Two or more responses combined	Potentially offers better adaptation to complex wound microenvironments.

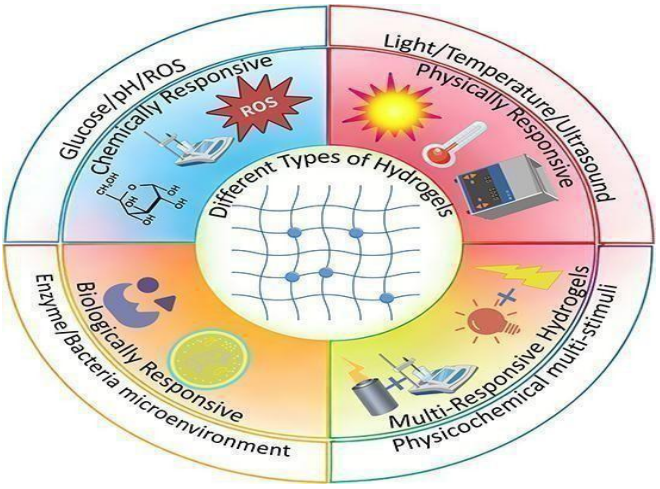

Figure 4: Types of Hydrogels

12. pH-RESPONSIVE DRUG DELIVERY

pH-responsive polymers contain ionisable groups whose charge state changes with environmental pH. This can modify electrostatic interactions within the polymer network, producing changes in chain expansion, water uptake, viscosity or permeability. In a wound delivery formulation, the pH response must be characterised experimentally across the pH range that the product is expected to encounter. A key design challenge is that wound pH is not constant. It may vary with wound age, infection, exudate and treatment. Therefore, the formulation should not be designed around a single assumed pH value without supporting measurements. Literature reviews emphasise the dynamic nature of the diabetic wound microenvironment and the opportunity to use pathological signals as triggers for smart materials. [2]
For the present project, 'pH-responsive' refers to the proposed mechanism of formulation response. It should not be assumed that any generic gel will automatically respond appropriately to a diabetic wound. Polymer selection, concentration, ionisation behaviour, gelation kinetics and drug-polymer interactions must all be investigated.

13. RATIONALE FOR THE PROPOSED SPRAY

Topical metformin has a growing preclinical evidence base for wound-healing-related effects [5,6].

Hydrogel systems can provide a hydrated local environment and serve as drug depots [2]. Responsive systems can change their properties according to wound-associated stimuli [2].

Sprayable systems can cover irregular surfaces and reduce the need for direct manipulation of fragile tissue; a metformin-containing thermosensitive spray has already been investigated experimentally [7].

Combining spray administration with pH-responsive gelation is therefore a rational formulationdevelopment hypothesis, but it requires direct experimental validation.

14. PREPARATION / DEVELOPMENT METHOD

A general laboratory development sequence may include the following steps:

1. **Preformulation:** assess metformin solubility, pH, polymer compatibility and possible interactions.
2. **Polymer screening:** prepare small batches with different candidate polymers or concentrations.
3. **Hydration:** allow polymer to hydrate completely under controlled mixing conditions.
4. **Drug incorporation**: prepare metformin solution and combine it with the hydrated controlled mixing.
5. **pH adjustment:** adjust formulation pH gradually and record the resulting pH and viscosity.
6. **Deaeration**: remove polymer phase using excessive entrapped air to improve filling and spray reproducibility.
7. **Filling:** transfer the trial formulation into a compatible spray container and actuator.
8. **Performance screening**: measure spray pattern, delivered mass/dose, viscosity, gelation time and gel strength.
9. **Release testing:** conduct an appropriate in-vitro release study using a validated method.
10. **Stability screening:** monitor appearance, pH, viscosity, drug content, spray performance and release behaviour under defined conditions.

15. EVALUATION PARAMETERS

Parameter	Purpose	Typical observation / output
Appearance	Detect visible instability	Colour, clarity/dispersion, sedimentation, phase separation
Homogeneity	Check uniform distribution	Absence of visible or aggregates non uniform regions
pH	Confirm formulation condition	Measured pH and change during storage.
Drug content	Verify assay	Percentage of labelled/target metformin content.

Content uniformity	Check batch reproducibility	Variation between samples / actuations.
Viscosity / rheology	Characterise spray and gel behaviour	Flow behaviour before and after trigger
Gelation time	Assess trigger response	Time required to reach defined gel state
Gel strength retention	Assess robustness after gelation	Resistance to deformation / erosion under test conditions.
Spray pattern	Assess coverage	Pattern shape, area and reproducibility
Delivered dose	Assess actuator performance	Mass or drug amount delivered per actuation.
Spreadability adhesion	Assess contact	Ability to cover and remain on a woundrelevant surface
In-vitro release	Characterise drug liberation	Cumulative drug released versus time.
Ex-vivo retention/permeation	Study local deposition	Drug retained in tissue versus permeated.
Microbial quality	Protect product quality	Microbial enumeration specified microbiological testing as applicable
Stability	Establishshelf-life behaviour	Change in physical, performance and attributes.

In-vitro drug release

An in-vitro release method should be selected according to the dosage form and scientific question. Common approaches include dialysis-based systems or diffusion cells. The method should be validatedfor sampling, sink conditions where relevant, drug recovery and analytical assay. Release data can be fitted to appropriate kinetic models only when the experimental design supports such interpretation.

Analytical estimation of metformin

A validated quantitative analytical method should be used for metformin assay and release testing. The method should demonstrate suitable specificity, accuracy, precision, linearity and robustness for the intended purpose. The exact analytical technique should be selected according to laboratory facilities and validated methodology.

Spray performance

Spray testing should consider actuation-to-actuation reproducibility, spray pattern, plume characteristics where relevant, delivered mass and drug content per actuation. Container orientation and storage conditions should be controlled because they may affect delivery.

Stability

Stability studies should monitor appearance, pH, viscosity/rheology, drug content, microbial quality where appropriate, spray performance and release characteristics. Any acceptance criteria must be justified for the intended product and study design.

16. QUALITY-BY-DESIGN CONSIDERATIONS

A quality-by-design approach can be used to connect material properties and manufacturing variables with product performance. For this formulation, critical quality attributes (CQAs) may include appearance, pH, viscosity, gelation behaviour, drug content, delivered dose, spray pattern, release profile, microbial quality and stability.

Development element	Examples for the proposed system
QTPP (Quality Target Product Profile)	Topical spray; reproducible metformin delivery; acceptable local tolerability; responsive gelation; adequate stability.
CQAs	pH, viscosity/rheology, drug content, delivered dose, spray pattern, gelation time, gel strength, release profile.
CMAs (material attributes)	Polymer grade, polymer concentration, metformin quality, excipient purity, water quality.
CPPs (process parameters)	Mixing speed/time, hydration time, order of addition, pH adjustment, temperature, filling conditions.
Risk assessment	Identify variables that may cause spray blockage, premature gelation, poor drug uniformity, instability or inadequate.
DoE	Use factorial/response-surface designs when enough preliminary information exists to optimise key variables.

A formulation should not be optimised only for maximum viscosity or maximum drug loading. The final balance should support sprayability, gelation, retention, release and safety simultaneously.

17. POTENTIAL ADVANTAGES

- Spray application may reduce the need for direct spreading over fragile tissue.
- Liquid-to-gel transformation may allow better coverage of irregular wound surfaces.
- A hydrated polymer network may provide a local drug depot and reduce immediate loss of formulation Responsive behaviour may allow formulation properties to change after contact with the wound environment.
- Metformin has an established pharmaceutical identity and extensive systemic-use history, while topical wound applications remain an area of active research.

The platform could potentially be adapted to other therapeutic agents after suitable compatibility and safety evaluation.

18. LIMITATIONS AND CHALLENGES

- Clinical evidence for topical metformin remains limited compared with the preclinical literature [5].
- A wound's pH is variable; a pH-responsive system may therefore show different behaviour between patients or at different stages of healing.
- Premature gelation could block the spray actuator, whereas inadequate gelation could cause poor retention. Polymer concentration affects both sprayability and gel strength; increasing one desirable property may worsen another.
- Local tolerability must be established because damaged tissue may be more sensitive than intact skin. Metformin-polymer interactions may affect drug availability and release.
- Packaging and actuator compatibility are essential for a spray product and may change during storage. Manufacturing scale-up can alter mixing, hydration and deaeration behaviour.
- Animal efficacy results cannot automatically be extrapolated to human diabetic ulcers.
- Regulatory requirements for a new topical wound-delivery product will depend on its exact composition, claims, route and jurisdiction.

19. FUTURE SCOPE

Future work can move from a single-stimulus formulation toward systems that integrate multiple wound signals. Recent literature describes pH-, glucose-, ROS- and enzyme responsive materials and increasingly multifunctional hydrogels designed to modulate infection, inflammation, oxidative stress and angiogenesis [3,4,12].

Optimise polymer composition using Design of Experiments.

Investigate pH response across clinically relevant wound conditions rather than one fixed pH.

Compare metformin alone with metformin-loaded responsive hydrogel and appropriate control formulations.

Study release, local tissue retention and cellular uptake using suitable in-vitro and ex-vivo models. Investigate antibacterial, antioxidant, anti-inflammatory and pro-angiogenic endpoints where scientifically justified.

Assess wound closure, histology, collagen organisation and vascular markers in validated animal models. Evaluate safety, irritation, sensitisation and local tissue compatibility.

Develop a reproducible spray container and actuator with reliable delivered dose. Conduct properly designed human studies before making clinical efficacy claims.

20. CONCLUSION

The development of a metformin-loaded pH-responsive in-situ gelling spray is a scientifically reasonable formulation research concept for diabetic wound management. The rationale is supported by three converging areas of literature: the biological need for improved diabetic wound therapy, growing preclinical evidence for topical metformin, and advances in responsive hydrogel technology [2 7]. The most important translational advantage of the proposed dosage form is the possibility of combining convenient spray application with a local gel depot. The formulation could potentially provide better surface coverage, local residence and controlled drug release. However, these are development goals, not established clinical outcomes. The pH-triggered mechanism, formulation composition, gelation behaviour, drug-release profile, local safety and therapeutic efficacy must all be experimentally demonstrated. Overall, the proposed system provides a suitable basis for a research review and can be developed further through preformulation studies, polymer screening, optimisation, pharmaceutical evaluation, preclinical wound-healing studies and ultimately controlled clinical investigation.

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