

**Formulation, Development and Evaluation of Amitriptyline-Loaded Polymeric Hydrogel for the Management of Diabetic Foot Ulcer**Varsha Rani<sup>1</sup>, Yogesh Kumar Garg<sup>2</sup><sup>1</sup>Research Scholar, Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, Rajasthan, India.<sup>2</sup>Professor, Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, Rajasthan, India.

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**Abstract:**

Diabetic foot ulcer (DFU) continues to be one of the most distressing and economically draining complications of diabetes mellitus, frequently ending in prolonged hospitalisation or lower-limb amputation when management is delayed. Persistent neuropathic pain, chronic low-grade inflammation and polymicrobial colonisation together sustain the wound in a non-healing state, and none of the dressings in routine clinical use address the neuropathic pain component directly. Amitriptyline, a tricyclic antidepressant long used for neuropathic pain, has additionally been shown to possess antibacterial and anti-inflammatory activity against organisms commonly recovered from chronic wounds. The present work was undertaken to formulate, develop and evaluate an amitriptyline-loaded polymeric hydrogel intended for topical application to diabetic foot ulcers, combining local analgesia, antimicrobial support and a moist wound-healing environment in a single dosage form. Hydrogels were prepared by the cold dispersion method using Carbopol 934 and hydroxypropyl methylcellulose (HPMC K4M) as the gelling polymers, with propylene glycol as co-solvent/humectant, and were optimised through a series of nine trial batches (F1–F9). The gels were evaluated for physical appearance, pH, spreadability, viscosity and rheological behaviour, gel strength, swelling index, drug content uniformity, in vitro drug release using the Franz diffusion cell, release kinetics, ex vivo skin permeation, antimicrobial efficacy against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, and short-term accelerated stability. The optimised batch (F6) containing 2% w/w Carbopol 934 and 1% w/w HPMC K4M showed a pH of  $5.6 \pm 0.2$ , a viscosity of  $18,450 \pm 340$  cP, and cumulative drug release of  $88.4 \pm 2.1\%$  over 12 hours, following a Korsmeyer–Peppas non-Fickian release pattern. The formulation retained acceptable physicochemical characteristics on storage at 40 °C/75% RH for 90 days. These findings suggest that an amitriptyline-loaded polymeric hydrogel is a technically feasible and promising adjunctive dosage form for the multimodal management of diabetic foot ulcers, warranting further ex vivo and in vivo confirmation.

**Keywords:** Amitriptyline; Polymeric Hydrogel; Diabetic Foot Ulcer; Carbopol 934; Drug Release Kinetics; Wound Healing.

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**1. Introduction**

Diabetes mellitus has quietly become one of the defining health burdens of this century. Global estimates place the number of adults living with diabetes at close to 589 million in 2024, a figure that is projected to keep climbing over the coming decades[1-5]. Among its many complications, the diabetic foot ulcer occupies an unusually cruel place: it develops slowly, often painlessly because of underlying neuropathy, and yet it is responsible for a disproportionate share of diabetes-related hospital admissions and lower-limb amputations[6,7]. Armstrong et al. note that diabetic foot ulcers precede the majority of non-traumatic lower-extremity amputations performed worldwide, and that roughly one in five affected patients will eventually require some level of amputation.

McDermott et al. add that the burden is not distributed evenly – it falls hardest on patients with longstanding, poorly controlled diabetes, and on populations with limited access to structured foot-care services[8-10].

The pathophysiology of a diabetic foot ulcer is rarely a single problem; it is a convergence of several. Sensorimotor neuropathy blunts protective sensation so that everyday trauma goes unnoticed; peripheral arterial disease starves the tissue of the oxygen and nutrients it needs to repair itself; and a persistently hyperglycaemic, pro-inflammatory local environment keeps the wound locked in the inflammatory phase of healing rather than allowing it to progress to proliferation and remodelling [11].

Left untreated, this combination invites bacterial colonisation, and once biofilm-forming organisms such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* establish themselves, the wound becomes still more resistant to healing and to antibiotic therapy[12,13]. It is telling that even with the current standard of care – debridement, offloading, glycaemic control and appropriate dressing selection – a substantial proportion of these ulcers still fail to close within a year, and recurrence after apparent healing remains common[14].

Wound care has moved way past plain gauze pads. Hydrogels have become super popular for treating wounds because they do things gauze simply cannot manage[15-20]. They keep the wound nicely moist, help gently clean away dead tissue, provide a soothing and cooling feel, and—most importantly—serve as a base where medicines can be mixed in to release slowly over time right at the site[21,22]. Materials like Carbopol, HPMC, and chitosan are heavily relied on to make these gel bases because human tissue tolerates them well, they are straightforward to work with, and they let manufacturers carefully control how thick the gel is, how easily it spreads, and how fast the drug gets released[23-25]. Because of this, hydrogels make fantastic carriers not just for fighting germs or helping tissue grow, but also for tackling a major part of wounds that often gets ignored pain[26].

People dealing with diabetic foot ulcers do not always feel pain in a standard way. Since nerve damage usually blocks normal pain signals, many patients still feel a very specific type of nerve-based discomfort, such as burning, tingling, or sharp shooting pains coming directly from damaged nerves underneath rather than from the outer wound itself[27,28]. Amitriptyline is an antidepressant that has been prescribed by mouth for decades specifically to treat this kind of nerve pain[29]. Its chemical action—blocking how the body reabsorbs noradrenaline and serotonin while also blocking sodium channels—makes it a great fit for the job. What a lot of people do not realize is that amitriptyline also fights bacteria on its own[30-32]. Research shows that amitriptyline and similar drugs display clear activity against tough bacteria like carbapenemase-producing *Klebsiella pneumoniae* and can even team up with colistin to boost its power. Other studies also point out that these drugs can lower specific inflammatory proteins like TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 that trap long-lasting wounds in an endless cycle of inflammation[33-35].

Taking amitriptyline by mouth to treat a spot on the foot is inefficient and exposes the patient to unwanted whole-body side effects like sleepiness and dry mouth[36]. Putting the medicine straight onto the wound using a hydrogel, however, could theoretically handle local pain, help fight off bacteria, and calm down inflammation all at once

without flooding the rest of the body with drugs[37,38]. Previous tests have already proven that amitriptyline can pass through the skin at solid levels when mixed with basic liquid solvents, which strongly supports the idea that putting it into a hydrogel dressing is entirely doable[39,40].

### Objectives

- The overarching aim of this study was to formulate, develop and evaluate an amitriptyline-loaded polymeric hydrogel suitable for the topical management of diabetic foot ulcers. The specific objectives were as follows:
- To carry out pre-formulation studies on amitriptyline hydrochloride, including solubility profiling, melting point determination and drug–excipient compatibility testing by Fourier-transform infrared (FTIR) spectroscopy.
- To formulate amitriptyline-loaded hydrogels using Carbopol 934 and HPMC K4M, individually and in combination, across a series of trial batches of varying polymer concentration.
- To evaluate the physicochemical properties of the prepared hydrogels, including physical appearance, pH, spreadability, viscosity, rheological behaviour, gel strength and swelling index.
- To determine drug content uniformity and to study in vitro drug release using the Franz diffusion cell, along with the kinetics and probable mechanism of drug release.
- To assess ex vivo permeation of amitriptyline across excised skin and to evaluate the antimicrobial efficacy of the optimised formulation against representative wound pathogens.
- To select an optimised batch on the basis of the above parameters and to subject it to short-term accelerated stability testing and skin-irritation assessment.

### Materials and Methods

#### Materials:

Amitriptyline hydrochloride (analytical grade, assay  $\geq 99\%$ ) was procured as a gift sample from a licensed pharmaceutical supplier. Carbopol 934, hydroxypropyl methylcellulose (HPMC K4M), propylene glycol, triethanolamine, methylparaben, propylparaben and disodium edetate were procured from standard laboratory chemical suppliers and were of pharmaceutical or analytical grade. Distilled water was used throughout. All other reagents used in analytical work, including those for high-performance liquid chromatography (HPLC), were of HPLC or analytical grade.

**Pre-formulation Studies:** Pre-formulation work began with a straightforward organoleptic evaluation of the drug (colour, odour, physical form), followed by melting point determination using the capillary method and confirmation of identity by FTIR spectroscopy, in which the spectrum of the pure drug was compared with reference data. Aqueous solubility was determined by the shake-flask method at  $32 \pm 0.5^\circ\text{C}$ , chosen to approximate skin surface temperature, and saturation solubility was also determined in phosphate buffer at pH 5.5, 6.8 and 7.4 to mimic the range of pH conditions likely to be encountered at a wound surface. Drug–excipient compatibility was assessed by preparing 1:1 physical mixtures of amitriptyline hydrochloride with each excipient, storing them at  $40 \pm 2^\circ\text{C}/75 \pm 5\%$  RH for four weeks, and comparing the FTIR spectra and visual appearance of the mixtures before and after storage for evidence of interaction.

#### Formulation of the Hydrogel:

Hydrogels were prepared by the cold dispersion method. Carbopol 934 was sprinkled slowly over

distilled water under continuous mechanical stirring (500 rpm) and allowed to hydrate for 12 hours to ensure complete swelling before use. Where HPMC K4M was included, it was dispersed separately in hot water ( $80^\circ\text{C}$ ) and cooled to room temperature prior to incorporation, following the standard cold–hot dispersion technique for cellulose ethers. Amitriptyline hydrochloride was dissolved separately in a propylene glycol–water mixture and was incorporated into the polymer dispersion with gentle stirring to minimise air entrapment. Methylparaben and propylparaben were used as preservatives and disodium edetate as a chelating agent. The pH of the Carbopol-containing batches was adjusted to 5.5–6.0 using triethanolamine, added dropwise with continuous stirring until a clear, uniform gel was obtained. Nine trial batches (F1–F9) were prepared by varying the polymer type and concentration, as summarised in Table 1, keeping the amitriptyline concentration fixed at 2% w/w across all batches so that the effect of the polymer system on gel behaviour and drug release could be assessed independently of dose.

**Table 1: Composition of trial batches F1–F9 of amitriptyline-loaded polymeric hydrogel (all batches also contained 0.2% w/w methylparaben, 0.02% w/w propylparaben and 0.05% w/w disodium edetate, with triethanolamine added q.s. to adjust pH).**

| Batch | Carbopol 934 (% w/w) | HPMC K4M (% w/w) | Propylene glycol (% w/w) | Amitriptyline HCl (% w/w) | Water (q.s. to) |
|-------|----------------------|------------------|--------------------------|---------------------------|-----------------|
| F1    | 1.0                  | -                | 10                       | 2                         | 100 g           |
| F2    | 1.5                  | -                | 10                       | 2                         | 100 g           |
| F3    | 2.0                  | -                | 10                       | 2                         | 100 g           |
| F4    | -                    | 2.0              | 10                       | 2                         | 100 g           |
| F5    | -                    | 3.0              | 10                       | 2                         | 100 g           |
| F6    | 2.0                  | 1.0              | 10                       | 2                         | 100 g           |
| F7    | 1.5                  | 1.5              | 10                       | 2                         | 100 g           |
| F8    | 1.0                  | 2.0              | 10                       | 2                         | 100 g           |
| F9    | 2.5                  | 0.5              | 10                       | 2                         | 100 g           |

#### Evaluation of the Hydrogel:

Physical appearance, colour, homogeneity and the presence or absence of grittiness were assessed visually and by touch. pH was measured using a calibrated digital pH meter, with the electrode dipped directly into the gel, in triplicate for each batch. Spreadability was determined by the parallel-plate method, in which a fixed quantity of gel was sandwiched between two glass slides, a standard weight was placed on the upper slide, and the diameter of the spread gel was measured after one minute; larger diameters indicated better spreadability. Viscosity and rheological behaviour were studied using a Brookfield-type rotational viscometer fitted with an appropriate spindle, at a range of shear rates from 0.5 to 100 rpm, to construct shear stress–shear rate plots and to classify the flow behaviour of each batch (Newtonian versus shear-thinning/pseudoplastic). Gel strength was assessed

by measuring the time taken for a weighted plunger to sink through a fixed distance of gel under its own weight. Swelling index was determined gravimetrically by placing a weighed quantity of gel in phosphate buffer pH 7.4 at  $37^\circ\text{C}$  and recording the increase in weight at fixed time intervals until equilibrium was reached.

Drug content uniformity was determined by dissolving an accurately weighed quantity of gel in methanol, filtering, diluting appropriately, and assaying spectrophotometrically at the wavelength of maximum absorbance for amitriptyline, cross-checked against an HPLC method for the optimised batch. In vitro drug release was studied using a Franz diffusion cell fitted with a dialysis membrane (molecular weight cut-off 12,000–14,000 Da), with phosphate buffer pH 7.4 maintained at  $37 \pm 0.5^\circ\text{C}$  in the receptor compartment and continuously stirred, following the general approach described for

topical semisolid formulations by Bhatia. Samples were withdrawn from the receptor compartment at predetermined time points over 12 hours, with immediate replacement of an equal volume of fresh buffer, and were assayed spectrophotometrically. The cumulative percentage drug release was plotted against time, and the resulting data were fitted to zero-order, first-order, Higuchi and Korsmeyer–Peppas kinetic models to identify the best-fitting model and the probable mechanism of release, on the basis of the correlation coefficient ( $R^2$ ) obtained for each model and, where the Korsmeyer–Peppas model was the best fit, the release exponent ( $n$ ).

Ex vivo permeation of the optimised batch was studied using excised full-thickness skin, mounted on the Franz diffusion cell in place of the synthetic membrane, under otherwise identical conditions, in order to obtain a more physiologically relevant estimate of permeation flux and lag time. Antimicrobial efficacy of the optimised batch was evaluated by the agar well diffusion method against *Staphylococcus aureus* (ATCC 25923) and *Pseudomonas aeruginosa* (ATCC 27853), two organisms frequently isolated from infected diabetic foot ulcers, with zones of inhibition compared against a drug-free (blank) hydrogel and a positive control. Skin irritation potential was assessed using the Draize patch test method in a small cohort of healthy rabbits in accordance with standard institutional animal ethics procedures, with erythema and oedema scored at 24, 48 and 72 hours after patch removal. Short-term accelerated stability studies were carried out on the optimised batch,

packed in collapsible aluminium tubes, stored at  $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$  for 90 days, with samples withdrawn at 0, 30, 60 and 90 days and re-evaluated for physical appearance, pH, viscosity and drug content.

## Results

The pure drug and its physical mixtures with the selected excipients showed no new peaks or loss of characteristic peaks in the FTIR spectra after four weeks of accelerated storage, and no discolouration or liquefaction was observed, indicating that amitriptyline hydrochloride was compatible with the polymers and other excipients used in this study. Aqueous solubility of amitriptyline hydrochloride was found to be high, consistent with its use as the hydrochloride salt, while solubility of the free base fraction decreased with increasing pH, in line with previously reported behaviour for the molecule.

Table 2 summarises the physicochemical evaluation of the nine trial batches. All batches were homogeneous, free from grittiness, and translucent to pale yellow in colour. Batches formulated with Carbopol 934 alone (F1–F3) produced clear gels with good gel strength but comparatively poor spreadability at higher polymer concentrations, while batches formulated with HPMC K4M alone (F4–F5) were easier to spread but showed weaker gel structure and a tendency toward syneresis on storage. The combination batches (F6–F9), containing both Carbopol 934 and HPMC K4M, gave the most balanced profile of spreadability, viscosity and gel strength.

**Table 2: Physicochemical evaluation of trial batches F1–F9 (mean  $\pm$  SD,  $n = 3$ ). CDR = cumulative drug release.**

| Batch | pH            | Viscosity (cP)   | Spreadability (g.cm/sec) | Swelling index (% , 6 h) | Drug content (%) | CDR at 12 h (%) |
|-------|---------------|------------------|--------------------------|--------------------------|------------------|-----------------|
| F1    | $5.4 \pm 0.1$ | $9,120 \pm 210$  | $6.2 \pm 0.4$            | $142 \pm 8$              | $96.8 \pm 1.5$   | $58.2 \pm 2.4$  |
| F2    | $5.5 \pm 0.2$ | $13,860 \pm 260$ | $5.1 \pm 0.3$            | $128 \pm 6$              | $97.2 \pm 1.1$   | $64.7 \pm 3.0$  |
| F3    | $5.6 \pm 0.1$ | $19,340 \pm 300$ | $3.9 \pm 0.3$            | $110 \pm 7$              | $95.9 \pm 1.8$   | $55.6 \pm 2.7$  |
| F4    | $6.0 \pm 0.2$ | $6,480 \pm 180$  | $9.8 \pm 0.5$            | $168 \pm 9$              | $94.3 \pm 2.0$   | $92.1 \pm 2.2$  |
| F5    | $6.1 \pm 0.1$ | $8,950 \pm 200$  | $8.4 \pm 0.4$            | $155 \pm 8$              | $93.7 \pm 1.6$   | $96.8 \pm 1.8$  |
| F6    | $5.6 \pm 0.2$ | $18,450 \pm 340$ | $7.0 \pm 0.3$            | $134 \pm 6$              | $98.6 \pm 1.2$   | $88.4 \pm 2.1$  |
| F7    | $5.7 \pm 0.1$ | $16,220 \pm 280$ | $7.4 \pm 0.4$            | $138 \pm 7$              | $97.9 \pm 1.4$   | $84.0 \pm 2.5$  |
| F8    | $5.9 \pm 0.2$ | $12,780 \pm 250$ | $8.1 \pm 0.3$            | $146 \pm 8$              | $96.5 \pm 1.7$   | $90.3 \pm 2.0$  |
| F9    | $5.5 \pm 0.1$ | $21,600 \pm 360$ | $3.2 \pm 0.2$            | $101 \pm 5$              | $95.1 \pm 2.1$   | $49.8 \pm 2.9$  |

Batch F6, containing 2% w/w Carbopol 934 and 1% w/w HPMC K4M, was selected as the optimised formulation on the basis of its pH ( $5.6 \pm 0.2$ , close to the physiological pH of intact and healing skin), acceptable viscosity and spreadability, satisfactory gel strength, and the highest drug content uniformity ( $98.6 \pm 1.2\%$ ) among the nine batches. Rheological study of F6 showed shear-thinning (pseudoplastic) flow with no evidence of thixotropic hysteresis, a behaviour generally considered desirable for topical semisolids because it allows the gel to spread easily

under the shear of application while regaining viscosity once shear is removed, helping the gel to remain in place on an irregular wound surface.

In vitro drug release from F6 reached  $88.4 \pm 2.1\%$  cumulative release at 12 hours, compared with  $64.7 \pm 3.0\%$  for the Carbopol-only batch F2 and  $96.8 \pm 1.8\%$  for the HPMC-only batch F5, which released its drug load more rapidly but with visibly poorer gel integrity on the membrane. Fitting of the release data showed the highest correlation coefficient for the Korsmeyer–Peppas model ( $R^2 = 0.989$ ) among the

models tested, with a release exponent ( $n$ ) of 0.68, indicating a non-Fickian (anomalous) transport mechanism in which drug diffusion through the swollen polymer matrix and gradual polymer relaxation/erosion both contribute to the overall release process. The Higuchi model also gave a reasonably strong fit ( $R^2 = 0.971$ ), consistent with a diffusion-dominated release process overall.

Ex vivo permeation of amitriptyline from F6 across excised skin showed a lag time of approximately 1.2 hours followed by a steady permeation flux, with total cumulative permeation over 12 hours lower than the in vitro release figure, as would be expected given the additional barrier presented by the stratum corneum; this is consistent with the general pattern reported for topical amitriptyline formulations delivered from simple co-solvent vehicles. Antimicrobial testing showed that F6 produced clear zones of inhibition against both *Staphylococcus aureus* and *Pseudomonas aeruginosa*, whereas the drug-free blank hydrogel produced no measurable zone, supporting the expectation that amitriptyline retains antibacterial activity when incorporated into the polymer matrix. Skin irritation testing showed no erythema or oedema at any time point in the treated group, and the primary irritation index was classified as negligible, suggesting that the optimised formulation is unlikely to cause local irritation on intact or peri-wound skin.

On accelerated stability testing, batch F6 retained its physical appearance, pH and viscosity within acceptable limits over the 90-day study period, with drug content remaining above 95% of the initial value at every time point tested. No visible phase separation, discolouration or microbial contamination was observed, indicating that the formulation is likely to be reasonably stable under the storage conditions tested, though longer-duration and real-time stability studies would be needed before any claim of shelf life could be made with confidence.

## Discussion

The evaluation of this study clearly shows that combining Carbopol 934 and hydroxypropyl methylcellulose (HPMC K4M) into a single composite hydrogel creates a highly practical and effective delivery system for applying amitriptyline topically to wounds. When looking closely at how these polymers behave individually, the reasoning behind blending them becomes very apparent. Using Carbopol by itself results in a gel that is mechanically very strong, but it tends to feel quite tacky and spreads rather slowly across a surface. On the other hand, using HPMC alone means the material spreads very easily, but it forms a much weaker gel network that is prone to leaking liquid, especially once a hydrophilic drug is mixed into it. By bringing these two materials together, the

formulation takes advantage of their complementary flow characteristics, successfully overcoming their individual shortcomings to produce a much more clinically useful wound dressing.

Looking closely at the physical behavior of the optimized hydrogel batch, it displays a distinct pseudoplastic, or shear-thinning, flow property. This is not just a minor technical detail; it has massive practical value in a real-world clinical setting. Because the dressing temporarily thins out under the mechanical pressure of a gloved finger or a spatula, it allows a caregiver to apply and spread the gel smoothly and evenly across the rough, uneven, and often deeply undermined surface of a diabetic foot ulcer. Furthermore, the lack of significant thixotropic hysteresis means that the internal structure of the gel bounces right back and firms up immediately after the application pressure is removed. This quick recovery ensures that the dressing stays right where it was put, preventing it from slumping, running off, or migrating away from the wound bed while the patient goes about their day.

When analyzing how the medication is actually released from this matrix, the study highlights a Korsmeyer-Peppas release exponent of 0.68 for the optimized batch. This specific figure places the release mechanism firmly into the non-Fickian, anomalous transport category. In plain terms, this means that the drug escapes the gel not just through simple molecular diffusion, but through a combination of diffusion through the swollen network and the gradual relaxation and breakdown of the polymer chains themselves. This dual action turns out to be ideal for a wound dressing. If a dressing relied entirely on simple diffusion from a rigid matrix, it could easily end up under-delivering the medication as the outer edges began to dry out near the wound margins. Instead, having a controlled erosion component ensures that the drug is released steadily and consistently as the dressing absorbs wound fluid over time.

Finally, one of the most intriguing discoveries of the work is that the drug-loaded hydrogel created clear zones of inhibition when tested against both *Staphylococcus aureus* and *Pseudomonas aeruginosa*, while the blank, drug-free gel showed no such effect. Since amitriptyline is primarily known as an antidepressant, this antimicrobial capability is an unexpected and welcome bonus. Proving that the drug retains its antibacterial properties even after being locked inside the Carbopol-HPMC polymer matrix means the formulation provides a powerful double benefit. It offers local pain relief for stubborn neuropathic discomfort while simultaneously delivering localized antimicrobial support to help fight off the persistent, difficult bacteria that so often cause chronic wounds to stall and fail to heal.

## Conclusion

An amitriptyline-loaded polymeric hydrogel was successfully formulated using a combination of Carbopol 934 and HPMC K4M, and was evaluated across the range of physicochemical, rheological, release-kinetic, antimicrobial and preliminary tolerability parameters expected of a topical wound-care dosage form. The optimised batch (F6) showed an appropriate pH, acceptable viscosity and spreadability, pseudoplastic flow behaviour, sustained drug release over 12 hours following a non-Fickian release mechanism, retained antibacterial activity against two clinically relevant wound pathogens, and no evidence of skin irritation in the model tested, with reasonable stability over a 90-day accelerated study. These findings suggest that a polymeric hydrogel is a feasible and rational vehicle for delivering amitriptyline directly to the diabetic foot ulcer bed, potentially combining local analgesia, adjunctive antimicrobial activity and a favourable moist-wound-healing environment within a single, patient-friendly dressing. Confirmation of this potential will depend on further ex vivo exudate-interaction studies, in vivo evaluation in a diabetic wound model, and, in time, appropriately controlled clinical investigation.

## Limitations and Future Scope

This study was limited to laboratory-scale formulation and in vitro/ex vivo evaluation; no in vivo wound-healing efficacy data are presented. Future work should extend to a validated diabetic animal wound model to confirm healing outcomes, histopathological changes and any effect on wound-associated pain behaviour; should include clinical wound isolates rather than reference strains in antimicrobial testing; should evaluate the gel's behaviour under simulated exudate loading over a realistic wear period; and should assess systemic absorption of amitriptyline following repeated topical application to a compromised skin barrier, given the drug's central nervous system activity when absorbed systemically. Scale-up and long-term (real-time) stability studies, along with sterility assurance appropriate to a wound-contact product, would also be required before any clinical translation could be considered.

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