Innovative Topical Gel Formulation: Fusidic Acid and Diclofenac Microparticles for Enhanced Wound Healing

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ABSTRACT
Wound healing is an intricate biological process involving a coordinated interplay of cellular, molecular, and biochemical events to restore tissue integrity. Topical Drug delivery systems have garnered considerable attention for their capability for localized and sustained release, minimizing systemic side effects. This study presents a novel gel formulation incorporating fusidic acid and diclofenac-loaded micro particles to enhance wound healing. Fusidic acid serves as a potent antibacterial agent, while diclofenac offers anti-inflammatory properties, together addressing two critical aspects of wound care: infection control and inflammation management. The gel matrix ensures prolonged drug retention and controlled release, promoting re-epithelialization and tissue regeneration. In vivo wound closure studies conducted on a murine excisional wound model revealed that wounds treated with the micro sponges gel showed significant wound contraction, with the percentage closure increasing from 10.05% on day 4 to 90.51% by day 21, compared to 9.68% in the untreated control group and 97% in groups treated with individual standard drug formulations by day 21. These findings underscore the synergistic potential of fusidic acid and diclofenac microsponge in accelerating wound healing and highlight the formulation as a promising candidate for clinical application in wound management. Further studies are warranted to evaluate its efficacy in chronic and infected wounds.

1. INTRODUCTION

Microsponges are polymeric drug delivery devices with porous structures **(Kaity *et al.*, 2010; Nacht and Katz, 1990).** These are minute, porous, sponge-like spherical particles with surface areas ranging from 5 to 150 nm. Microsponges have several merits, including high entrapment efficiency and capability of being stable at high pH and temperatures. Because of their porous structure, the release of medicaments can be prolonged **(Jain *et al.*, 2011).** Microsponges encapsulate the drug, allowing controlled release and prolonged drug delivery duration **(Cho *et al.*, 2014)** Wound healing is an intricate biological process that progresses through overlapping phases of haemostasis, inflammation, proliferation, and remodelling, orchestrated by cellular and molecular mechanisms **(Kumar and Ghosh, 2015)**. Ensuring rapid and effective wound closure with minimal complications is a significant challenge in clinical medicine. Persistent wounds often associated with microbial infections and inflammatory responses, contribute to delayed healing, elevated healthcare costs, and increased patient morbidity **(Das & Baker, 2016).** To address these challenges, the development of advanced topical formulations with multifunctional properties—antimicrobial, anti-inflammatory, and pro-regenerative—has garnered substantial research interest. Fusidic acid, a steroidal antibiotic, exhibits strong efficacy against Gram-positive bacteria, including *Staphylococcus aureus*, a common pathogen in wound infections. **(Ribeiro *et al.*, 2020)**. Its inclusion in topical therapies enhances wound healing outcomes by eradicating infections, thereby reducing inflammation. Similarly, diclofenac, an extensively used non-steroidal anti-inflammatory drug (NSAID), modulates inflammation and pain at the site of injury, promoting the proliferative and reparative phases of wound healing **(Kuhn & Scharffetter-Kochanek, 2020)**. The synergistic application of these agents offers a promising therapeutic approach. Encapsulation of these bioactive agents into micro particles integrated within a gel formulation provides additional advantages over conventional topical applications **(Hussain *et al.*, 2014).** Microparticle technology facilitates controlled and sustained drug release, ensuring therapeutic concentrations at the wound site while minimizing systemic exposure and reducing the risk of side effects **(Patel *et al.*, 2021)**. Moreover, a hydrogel-based vehicle can offer enhanced wound coverage, maintain a moist wound environment, and ensure prolonged residence time for the active components **(Boateng *et al.*, 2008)**. This study emphasizes the exploration of formulation and evaluation of an innovative topical gel embedding

fusidic acid and diclofenac-loaded microsponges. By combining the antimicrobial and anti-inflammatory effects of these agents with the biophysical advantages of microparticle and gel technologies, this formulation is poised to enhance wound healing efficacy. The findings have implications for developing cost-effective, patient-compliant therapies targeting various wound etiologies.

2. MATERIAL AND METHOD

2.1 Formulation of Microsponges via Quasi emulsion method

The formulation of microsponges was accomplished by the quasi-emulsion solvent diffusion technique. The dispersed phase, which contained ethyl cellulose polymer and triethyl citrate (1% w/v) as a plasticizer, was dissolved in a 1:1 mixture of dichloromethane (DCM) and ethanol. Simultaneously, the continuous phase, containing polyvinyl alcohol (PVA) as a surfactant, was dissolved in water. The inner phase was gradually introduced into the continuous phase under constant stirring using a magnetic stirrer for 60 minutes. The final mixture was filtered, rinsed three times with distilled water, and dried overnight in a calcium chloride desiccator **(Bhatia and Saini, 2018)**. All the other characteristics and the evaluatory section already has been published in African Journal of biomedical research Vol. *27(4s) (November 2024); 1558 – 1567*. This is the in-vivo section for the study.

2.2 Animals required

The animals Wistar Rat (procured from in-house animal facility of PBRI) weighing 200-250g were kept in standard large spacious hygienic polypropylene cages and maintained at 22 ± 2 ◦C temperature with 12/12-h light and dark cycle. All the animals were fed with commercially available rat normal pellet diet (NPD) purchased from Keval Sales Corporation, Vadodara and water ad libitum was provided up to the end of the study.

2.3 *In-vivo* wound healing activity

The procedure for assessing wound healing activity in rats involves several key steps. Initially, healthy rats are selected and anesthetized to minimize discomfort. A designated area on the dorsal side of each rat is shaved and cleaned, and a full-thickness excision wound is carefully created using a surgical blade. Following wound induction, the animals are assigned to various groups, including a normal control group and a negative control group (inducer group), a positive control group (treated with a standard wound-healing agent such as 2% Mupirocin ointment), and the test group, which receives the experimental treatment (Microsponges gel formulation). The wound area for each rat is measured on specific days (e.g., days 0, 3, 7, 14, and 21) using a digital calliper, and the percentage of wound closure is calculated based on the initial wound size **(Pandit *et al.*, 2017; Patole *et al.*, 2023).** The wounds are observed daily for signs of infection or healing, and the respective treatments are applied topically to the wound area according to the group assignments. Throughout the study, body weight, wound contraction rate, and general health are monitored. On the final day of observation, the percentage of wound closure is determined by comparing the healed area to the original wound size. This method allows for a quantitative evaluation of wound healing progression and the efficacy of the test treatments in promoting wound closure (**Ko *et al.*, 2005; Sambrekar *et al.*, 2011**). We calculated the percentage of wound contraction applying the following formula.

$$Percentage\ of\ wound\ contraction = \frac{Initial\ wound\ area - Specific\ day\ wound\ area}{Initial\ wound\ area} \times 100$$

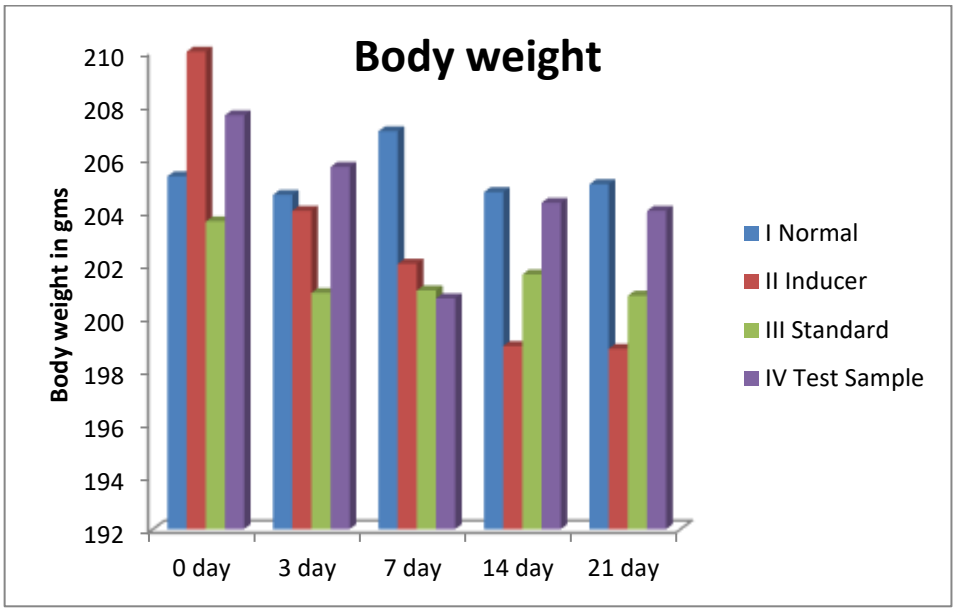
The animals were randomly assigned to four groups, with each group consisting of six animals.
Group I: Normal Group.
Group II: Inducer group
Group III: 2% Mupirocin ointment gel (Reference Standard Marketed Preparation).
Group IV: Test group treated with (Microsponges gel containing Fusidic acid and Diclofenac)

3. RESULTS

3.1 Body Weight

Table 1: Body Weight (gm)

S. No.	Group	Body Weight (cm)				
		0 day	3 day	7 day	14 day	21 day
I	Normal	205.3±6.082	204.6±6.082	207±4.725	204.7±7.010	205±6.082
II	Inducer	210±5.010	204±6.082	202±6.806	198.9±6.244	198.8±7.211
III	Standard	203.6±7.211	200.9±9.539	201±9.451	201.6±8.888	200.8±10.40
IV	Test Sample	207.6±10.40	205.6±10.21	200.7±16.50	204.3±12.05	204±8.717*



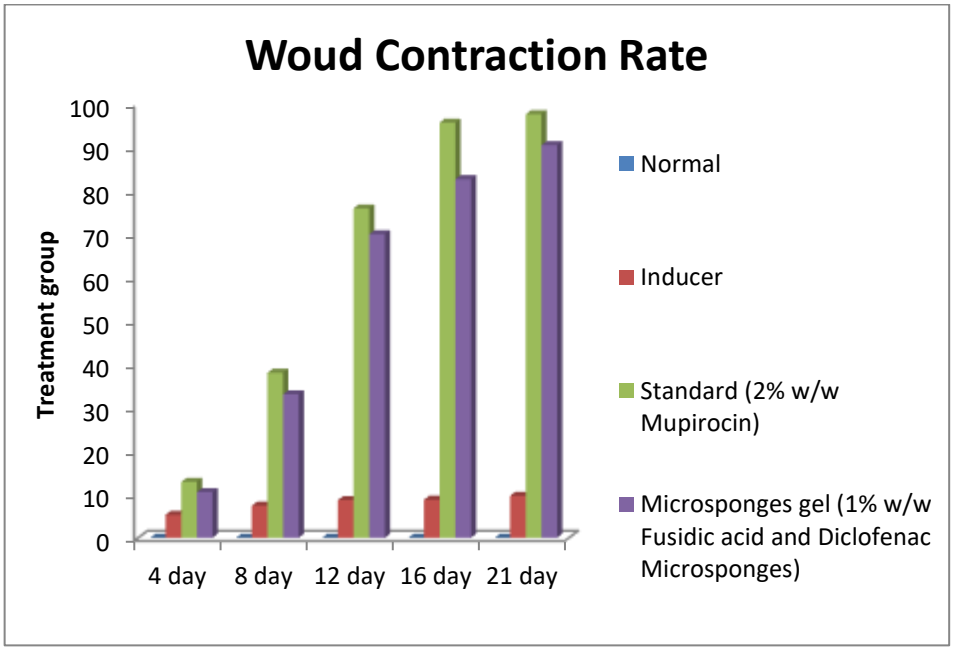
Graph 1 Body Weight Assessment

3.2 Wound contraction studies

Wound contraction is an essential parameter for evaluating wound healing. The results demonstrating significant wound contraction are presented in the table.

Table 2: Percentage of wound closure across different treatment groups

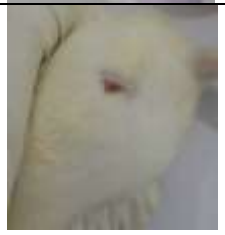
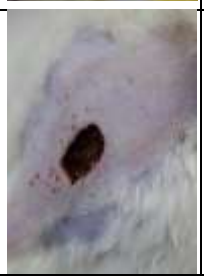
Sr. No	Formulation	Percentage of wound healing during different days of observation (%)				
		4 day	8 day	12 day	16 day	21day
1	Normal	0	0	0	0	0
2	Inducer	5.31±0.7123	7.42±0.8144	8.68±0.7824	8.78±0.8849	9.68±0.9810
3	Standard (2% w/w Mupirocin)	12.89±0.7437	38.05±0.7279	75.9±0.6429	95.68±0.6431	97.62±0.2523
4	Microsponges Gel (1% w/w Fusidic acid and Diclofenac Microsponges)	10.05±0.7823	33.08±0.5239	68.96±0.5519	82.65±0.5532	90.51±0.5824



Graph 2: Assessment of wound healing efficacy

3.3 Images of wound closure

Table 3: Visual representation of wound closure across different treatment groups

Group	0 Day	3 Day	7 Day	14 Day	21 Day
Normal					
Inducer					
Standard (2% w/w Mupirocinoint ment)					
Microsponges gel (1% w/w Fusidic acid and Diclofenac Microsponges)					

4. DISCUSSION

The body weight data presented in Table 1 reflects the impact of different treatment groups over a period of 21 days. The normal group (Group I) showed relatively stable body weight throughout the study, with minor fluctuations ranging from 205.6±6.082gm to 205±4.725gm. This suggests no significant alterations in the overall health status of the animals in this group. In contrast, the inducer group (Group II) exhibited a consistent reduction in body weight, starting from 210±5.010gm on day 0 to 198.8±7.211gm on day 21. This indicates a decline in the general health of the animals, likely due to the wound induction and the stress associated with the wound healing process. The reduction in body weight in the inducer group may also be linked to the metabolic changes that take place during wound healing, as the body redirects energy towards tissue repair. The standard group (Group III) treated with 2% w/w Mupirocin showed relatively stable body weight, similar to the normal group, with minor fluctuations, ending at 200.8±10.40gm on day 21. This suggests that the standard treatment did not negatively affect the overall health of the animals and have contributed to better wound healing, maintaining the animals' health status. The test group (Group IV) treated with microsponges gel (1% w/w Fusidic acid and diclofenac Microsponges) also exhibited relatively stable body weight, starting from 207.6±10.40gm on day 0 and ending at 204±8.717gm on day 21. While there was a slight decrease in body weight, the change was not significant. This suggests that the test formulation did not negatively impact the overall health of animals and tolerated the study period well. Overall, the body weight data indicates that while the inducer group experienced a notable reduction in body weight, the normal, standard, and test groups maintained relatively stable weights, reflecting the overall safety and tolerability of the test and standard treatments. The wound contraction data shown in Table 2 and Graph 2 showcase the effectiveness of various formulations in enhancing wound healing. In the normal group (Group I), there was no wound closure, as expected, since this group did not receive any wound or treatment. The inducer group (Group II) exhibited minimal wound closure, with a steady percentage closure of around 5.31% to 9.68% over the 21-day period. This suggests that without any therapeutic intervention, the wounds in this group failed to heal significantly. The standard group (Group III) treated with 2% w/w Mupirocin showed substantial wound contraction, with wound closure progressing from 12.89% on day 4 to 97.62% by day 21. This rapid wound closure demonstrates the effectiveness of Mupirocin as a standard wound healing agent, supporting its role in accelerating wound contraction and improving healing outcomes. The test group (Group IV), treated with gel containing 1% w/w Fusidic acid and Diclofenac Microsponges, also showed significant wound contraction, with the percentage closure increasing from 10.05% on day 4 to 90.51% by day 21. While the wound closure in the test group was slightly lower than the standard group, it still demonstrated a high level of efficacy, especially by day 21. The presence of Fusidic acid, an antibiotic, combined with the anti-inflammatory properties of diclofenac, likely contributed to the enhanced wound healing observed in this group. Overall, the wound contraction studies indicate that the microsponges gel formulation is effective in promoting wound healing, with results comparable to the standard Mupirocin treatment. The use of this formulation could provide a promising alternative for wound healing, particularly in cases where a combination of antimicrobial and anti-inflammatory action is beneficial. The body weight and wound contraction data collectively suggest that the Microsponges gel formulation is well tolerated and effective in enhancing wound healing, with results similar to the standard treatment. These findings support the potential use of microsponges gel as a novel therapeutic option for wound management. Images of wound closure would have documented the visual progress of healing across the treatment groups over the observation period.

5. CONCLUSION

The development of topical gel formulations containing fusidic acid and diclofenac-loaded microspheres is a significant advancement in wound healing therapy. These formulations ensure sustained and controlled drug release, enhancing therapeutic efficacy while minimizing side effects. Fusidic acid provides antibacterial action, while diclofenac has potent anti-inflammatory properties. The combination enhances bioavailability at the wound site, supports patient compliance, and reduces dosing frequency. The gel's consistency ensures prolonged contact with the skin, facilitating optimal drug delivery. This innovative approach aligns with the growing demand for advanced wound care technologies, offering a patient-centric solution for improved healing outcomes. Future studies should explore scalability, stability, and clinical performance to further establish their efficacy and safety in various wound types.

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