RESEARCH PAPER

Formulation, Optimization and Evaluation of Wound Healing activity of Lawsone-loaded Scaffold based gel for Topical Delivery

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ABSTRACT
The skin acts as a vital protective barrier and plays a crucial role in maintaining homeostasis, sensory perception, and defense against external pathogens. Disruption of skin integrity results in wound formation, which may be acute or chronic depending on the healing duration. Chronic wounds, particularly those associated with conditions such as diabetes and vascular disorders, present significant therapeutic challenges. In recent years, hydrogels have emerged as promising wound-healing biomaterials due to their structural similarity to the extracellular matrix, high water retention, flexibility, and ability to deliver therapeutic agents. In the present study, chitosan and polyvinyl alcohol (PVA)–based hydrogel scaffolds loaded with 2-hydroxy-1,4-naphthoquinone were developed using a freeze-drying technique. Various scaffold formulations were prepared by altering chitosan:PVA ratios and were evaluated for particle size, entrapment efficiency, in-vitro drug release, rheological behavior, and physicochemical properties. Optimization was carried out using a Central Composite Design (CCD) to study the influence of polymer concentrations on particle size and entrapment efficiency. Among the formulations, F4 (chitosan:PVA, 2:1) exhibited the highest entrapment efficiency (92.45 ± 0.15%) with an optimal particle size (148 ± 0.15 nm). The optimized formulation demonstrated sustained drug release over 12 hours, suitable pH for topical application, good spreadability, homogeneity, and pseudoplastic rheological behavior. Both in vivo wound-healing studies and histopathological examinations demonstrated that drug-loaded hydrogel–treated groups exhibited significantly enhanced re-epithelialization, collagen deposition, decreased inflammation, and improved granulation tissue formation compared with controls. In conclusion, the present work provides a promising chitosan/PVA hydrogel scaffold as an effective wound-healing system for prolonged topical delivery of 5-FU and enhancing healing response due to its high adhesion property combined with favourable biocompatibility.

Keywords: skin, wound-healing, spread ability, homogeneity, pseudoplastic, rheological behavior etc
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INTRODUCTION

The skin, the largest organ in the body, serves as a remarkably effective barrier between the internal environment and the external world. The skin is multifunctional and provides hydration, thermoregulation, sensation, fluid balance and protection from pathogens. If the external environment changes continuously for a long time, such internal balances will operate under extreme stress on this important organ, thus responding to many stimuli [1]. Disruption of skin integrity (e.g. creation of wounds) is a risk factor for many diseases. Great discomfort and agony from the development of wounds can occur, even in severe cases leaving an individual incapacitated. Wound can be classified as acute or chronic based on the duration of the healing process [2]. Acute wound are defined wounds that occur when the skin will break down from topical agents or trauma (i.e. surgical incision, bite) where they can heal themselves through normal expected mechanisms without external force; therefore termed "acute." Acute wounds generally take 8 to 12 weeks to heal. Chronic wounds are characterized by an inability to heal through the normal phases of repair within three months or longer, and usually non-healing wounds show a recurrent behaviour pattern. Well-treated or poorly treated acute injuries are the most common causes of these chronic wounds. Chronic and complicated wounds are usually related to some pathologies, such as diabetes mellitus and vascular disorders, which complicate the treatment process mainly due to the presence of more complex pathological pathways. [3] In the field of wound healing, Hydrogels are three-dimensional network which cure the disease because hydrogels have received attention in recent years as a result of their unique properties

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. Due to their unique properties, hydrogels have recently generated a lot of interest in the area of wound healing. Hydrogels are three-dimensional crosslinked polymeric networks. Physical crosslinking refers to those that are reversible or temporary, which are caused by polymer chain entanglement, ionic interactions, electron interactions and hydrogen bondings [4]. This allows the hydrogel to get back into solution when external conditions change. Chemical crosslinking involves chemical reactions that create a crosslinked three-dimensional structure using irreversible covalent links. Therefore, because of chemical crosslinking hydrogels they have a constant structure which is also very stable. These have excellent hydrophilicity, and after being in aqueous solutions, they do not lose their flexibility. Hydrogels are similar to biological tissues with the mesoscopic level of water content (up to 95%), deformability and porous structure. The first synthesis of hydrogels as biomaterials was invented by Wichterle and Lim in 1960 [5]. Methods The synthesized poly2-hydroxyethyl methacrylate (PHEMA) was used to prepare hydrogels, which were applied as a filler for eye evisceration operations and also as components in contact lenses. Hydrogels have multiple benefits due to their unique properties compared to traditional dressings in wound-healing applications. They can also alleviate patients' pain, ameliorate wound microenvironment, resist pathogens and facilitate healing at the same time. In addition, hydrogels can act as customized dispensing systems for drugs, proteins or even cells. The extracellular matrix (ECM), which is a molecular scaffold that surrounds cells, plays an important role in the work of creating an appropriate environment to promote re-epithelialization and angiogenesis during wound healing. Hydrogels have attracted much research attention and have broad applications across biological sciences owing to their structural similarity with extracellular matrix (ECM). However, the use of hydrogels has been recently limited either by more elaborate coverings (besides their physical surface coating) or by only isolating some capabilities. Functional hydrogels have been used to treat a variety of wound types. Hydrogels are complex biomaterials with special properties that make them suitable for pharmaceutical use [6]. Due to their analogies with actual tissues, ability to hold water, and promise for controlled drug delivery they are vitally employed in tissue engineering wound treatment and other biomedical fields. Current studies in this area continue to explore and improve the potential uses and potentials of hydrogels in health care [7].

MATERIAL AND METHODS

Procurement Statement

All chemicals, reagents, and pharmaceuticals referenced in this work were procured from reputable commercial sources with analytical grade purity. Subsequently, they were utilized in the investigations without further purification. Lecithin, have been purchased from Sigma- Aldrich in St. Louis, MO, USA. The lecithin quality was≥99%. Merck, located in Darmstadt, Germany, provided the sodium alginate and polyvinyl alcohol (PVA). The chitosan was sourced from SRL Chemicals in Mumbai, India, while the 2-hydroxy-1,4-naphthoquinone was obtained from TCI Chemicals in Tokyo, Japan.

Preparation of Chitosan/Polyvinyl alcohol (PVA) tissue scaffolds formulations

The scaffolds were produced using a freeze-drying technique. Specifically, 2% (w/v) polyvinyl alcohol and chitosan were solubilized in their corresponding concentrated solutions. To attain a gel-like consistency, these polymer dispersions were agitated for one hour at 200 rpm using a magnetic stirrer and thereafter allowed to rest for an additional hour. The chitosan and polyvinyl alcohol gels were subsequently combined in ratios of volume of 1:1, 1:2, 1:3, 2:1, 2:2, and 2:3, or physically blended for five minutes [8]. Subsequently, 0.5 mL of the gel mixes was dispensed into each well of a 24-well plate. To acquire crosslinked scaffolds, the mixtures were frozen at -20 ℃ for 24 hours and subsequently lyophilized for 24 hours at around -50 ℃. The scaffolds were equilibrated for two hours in a 5% (w/v) sodium tripolyphosphate aqueous solution, thereafter rinsed twice with distilled water, and lyophilized again to promote cross-linking. After preparing the scaffolds with concentrated formulations, the quantity of 2-hydroxy-1,4-naphthoquinone in each was ascertained to be 5 mg.

Table 1: Compositions and Particle size, zeta potential, and EE % of scaffolds formulation

Formulation Code	Chitosan /PVA	Particle size (nm)	Zeta potential (mV)	EE (%)
F-S1	1:1	173± 0.58	-39.65±0.83	82.99±0.05
F-S2	1:2	147± 0.34	-26.61±0.11	93.13 ± 0.43
F-S3	1:3	182± 0.67	-41.15±0.76	87.72 ± 0.65
F-S4	2:1	195± 0.13	-47.85±0.52	90.45 ± 0.13
F-S5	2:2	205± 0.54	-51.29 ±0.85	88.15 ± 0.75
F-S6	2:3	217± 0.71	-47.42 ±0.91	87.98 ± 0.21

Table:1 Compositions and Particle size and EE % of scaffolds formulation

A number of aspects, including the crosslinking method, the proportion of chitosan to PVA, the quantity of scaffolds, and the drug loading, were taken into careful consideration throughout the process of designing and formulating the scaffold. F4 selected best formulation for entrapment efficiency 92.45 ± 0.15 with particle size range 148± 0.15 [9].

Table 2:Regression analysis summary for responses Particle size and Entrapment Efficiency

Quadratic model	%CV	R^2	Adjusted R^2	Predicted R^2	SD
Particle size	0.4945	0.9990	0.9982	0.9927	0.7719
Entrapment Efficiency (EE)	2.70	0.9484	0.9116	0.6334	2.19
Particle size = +151.93+13.96*A+ +16.66*B+ +5.68*AB+4.24A^2+2.57* B^2.....Eq. (1)					
Entrapment Efficiency = +84.73+ 5.48*A+ +4.63*B+ 4.75*AB+ -3.05*A^2+ -3.05* B^2….Eq. (2)					

Table:2 Regression analysis summary for responses Particle size and Entrapment Efficiency

Optimization of Prepared Scaffolds

The Central Composite Design (CCD), an outcome surface tool, was utilized for estimating the impact of independent factors on dependent responses used by Expert Design (DoE) program (version 13.2.0.4, Stat-Ease, Minneapolis, MN, USA) to optimize scaffold batches according to independent and dependent factors. The selected independent variables for this formulation were Polyvinyl Alcohol (PVA) (%) and Chitosan (%), whilst the dependent responses were particle size (nm) and entrapment efficiency (EE) (%) [10].

Drug Content determination

After dissolving 10 mg of scaffolds in 100 ml of distilled water, 0.1 ml of the sample was extracted and diluted with 10 ml of water. Using a UV visible spectrophotometer and distilled water as a blank, the absorbance of this solution was measured at 286 nm (λmax).

Gel formation of prepared Scaffold formulation

Following the successful formulation of lawsone-loaded Scaffold, the vesicular dispersion was incorporated into a topical gel basis to enhance spreadability and skin retention [11]. Gel formulated with Carbopol.

***In-Vitro* Drug Release Studies**

The drug concentration was assessed spectrophotometrically after the filtration process of samples collected at time intervals. To maintain continuous sink conditions, the removed volume was replenished with fresh buffer. To examine release kinetics, a cumulative percentage of release has been determined and graphed over time [12].

***In Vivo* Study**

The Institutional Animal Ethics Committee approved the acquisition of all animal's protocol number: (IIMT/CMS/CPCSEA1297/IAEC/23-24/006) for the purposes of safety, effectiveness, and comparative research evaluation of viability, wellbeing, and comparable exploration of diverse injuries using distinct damage healing criteria. Dawley, Sprague Rats weighing between 150 and 250 grams on average were captured. Every experimental animal is housed in a lab in accordance with CPSCEA regulations. For the experimental animals, these are conventional protocols [13]. According to these criteria, the air humidity should be 55±5% and the standard temperature for experimental rats should be 25±2ºC. Rats remain in both light and dark phases in accordance with normal norms. This community's goal is to reduce pointless animal experiments. The 1960 Prevention of Cruelty to Animals Act (CPSCEA). This legislation mandates that animal cages and housing be hygienic and clean. Animals used in experiments should be fed appropriately and on schedule. There are usually bottles of drinking water in the animal enclosure. Every experimental animal operation adheres to the Institutional Animal Care and Use Committee's (IACUC) standards [15].

RESULT

The percentages of polyvinyl alcohol (PVA) and chitosan were chosen as the independent variables in the present formulation. Particle size (nm) and entrapment efficiency (EE) (%) were used as the dependent responses. the Central Composite Design (CCD), a response surface methodology approach, was the optimization design used to forecast how independent variables would affect dependent responses. displays the different levels or experimental ranges for the chosen independent variables[16]. it was found that all three dependent responses matched a polynomial quadratic model, with a non-significant lack of fit ($p > 0.05$). To evaluate how each dependent response interacted with two distinct independent factors, the CCD findings were shown as 3D response surface graphs (Figure 1). The thorough explanations of each answer are provided below:

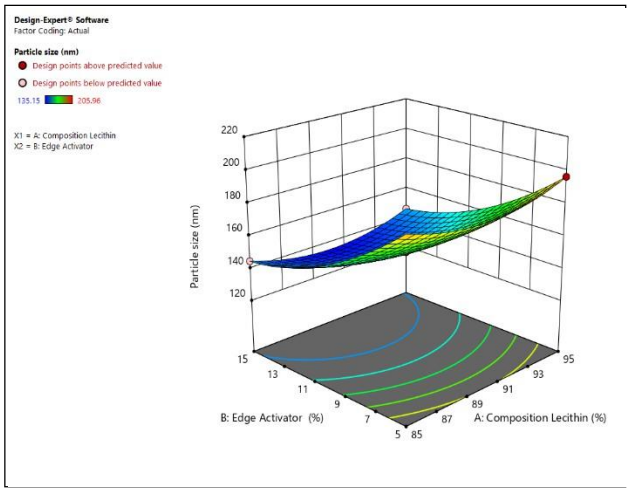

Figure 1: 3D response surface depicting the interaction effect of the independent variables like Composition Polyvinyl Alcohol (PVA) and Chitosan on (A) particle size and (B) Entrapment Efficiency.

Independent factors' impact on EE

The encapsulation efficiency (EE) was shown to be significantly influenced by the chitosan to PVA ratio; however, EE is also influenced by other parameters. The interactions between the ratios of chitosan to PVA were statistically significant ($P < 0.05$) for EE (Figure 1). Additionally, that all 13 formulations had EE values between 70 and 90. Following the evaluation of every variable, the formulation with an EE of 70-90 and a particle size of 132.42-194.28 nm was determined to be the best one [17].

In *Vitro* drug release

The in vitro release profiles of F1 to F6, which grow gradually and show different kinetic features released in 12 hrs At t=0 min, all formulations exhibit zero release, suggesting that the baseline is same. A rapid first burst (19.96% F1 to 19.76% F4) was recorded at 1 minute, suggesting that the drug was released from the matrix immediately. When compared to the other release values during the next several minutes, F3 exhibits the values at 12 hr (50.85±1.18%), F4 shows a comparatively fast release rate at all timepoints that indicating a higher permeability and a quicker rate of dissolution. With a maximum release of 73.65±1.21%, which may be explained by a sustained release mechanism [18].

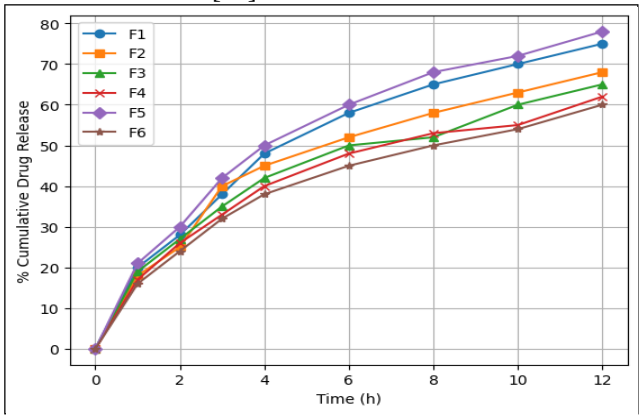

Figure 2: Graphical representation cumulative drug F1-F6

Visual andSensory Inspection of Prepared Formulations

Every hydrogel that was produced was light yellow in color. The color intensity was not significantly impacted by the hydrogel medium's varying lawsone concentration. However, the power of adhesion, stickiness, consistency, and fragrance vary depending on the kind of gelling agent used. Pictures of newly made hydrogels [19].

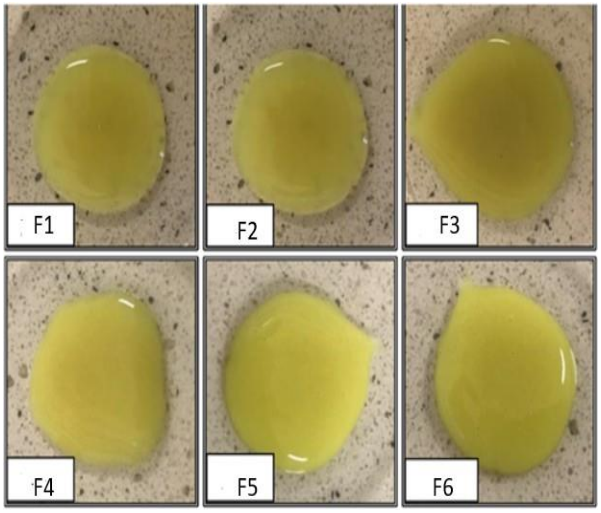

Figure 3.* Photographs *of prepared hydrogels. F1 (1:1), F2 (1:2), F3 (1:3), F4 (2:1) F5 (2:2), F6 (2:3)

pH Study

In accordance with the physiological pH of the skin, the pH values of the produced formulations varied from 4.45 ± 0.02 and 4.50 ± 0.04, 5.40 ± 0.01 and 5.90 ± 0.01, 6.51 ± 0.04, indicating that they can applied to the skin without causing irritation.

Spread ability Test

The spread ability affects that how evenly it distributes over the skin. The hydrogel's increased surface area under applied pressure serves as an indicator for this characteristic. The gel's evenly distributed application on the skin and patient compliance is made possible by its ease of spreading. Hydrogels based on spread ability 305.70 ± 6.70, 387.30 ± 12.06, 268.76 ± 3.17, 254.96 ± 0.92, 298.50 ± 5.73, 243.03 ± 5.13 were found [20].

Homogeneity

The Scaffold gel as prepared was visually checked for the homogeneity and found to be homogeneous [21].

Rheological studies

A number of formulations were found to operate as shear thinning systems. Pseudoplastic rheology states that shear stress rises with rotational velocity. The rheological analysis of the in-situ gelling system's preparation revealed that viscosity decreases as angular velocity increases shown in table 2 [21].

Table :2 Rheological studies of Scaffold gel after gelation

Shear Rate (RPM)	Viscosity of the formulation(cps)					
	F1	F2	F3	F4	F5	F6
10	1028	1345	2013	2548	2549	2619
20	1124	789	1350	1350	1358	1358
50	670	479	885	748	1079	1080
100	420	380	519	456	589	595

Table :2 Rheological* studies *of Scaffold gel after gelation

Histopathological studies

The histology on the zero and fourteenth test days after the impacts of constructive management and examination details. As a result of twisted imitation with various elements throughout the casing bandanna recovering technique, distinct times of twisted mending are occurring. According to a histopathology evaluation conducted during daylight hours on the third covering of the body, the emergence of a flaming cell is a completely superior disruption. After being removed, granulating tissues were stored in a 10% formalin solution. Samples were dried using a graded series of methanol or ethanol before being embedded in paraffin blocks for histopathological examination [24-26].

The tissue was cut into 5 mm thick slices using a sludge microtome, and the amount of collagen fibers and granulating tissue that were visible at the wound site was then assessed using Masson's trichrome and hematoxylin and eosin (H&E). Next, an optical microscope (Nikon Eclipse, 50ipol) was used to assess these data at a magnification of 40 X shown in figure 4 [27].

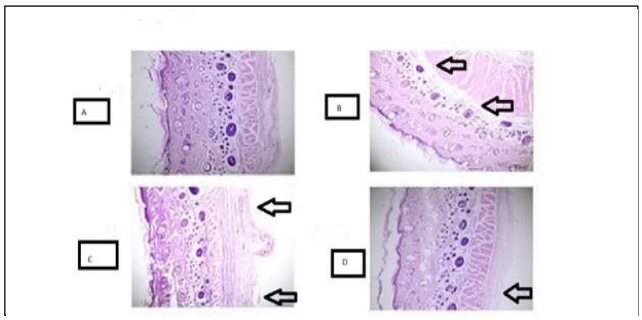

Figure: 4 Representative histology images of wound sections A) Normal Control group B)* Wound Control *C)* Standard Treatment *D) Drug loaded gel

Result & Discussion The findings on wound healing were further supported by the histological analysis of the various formulation-treated groups. Staining might be used to identify the inflammatory cells involved in this process and track the collagen and fibroblast. Microscopic histological examination, which includes the quantitative study of several variables, including inflammatory cells, epithelization, and granulation tissue production, was used to assess the improvement in healing. The H&E staining of the dissected tissues from each of the treated animal groups by day 14 after the injury, fewer inflammatory cells were being drawn to the wound site. The negative control group had substantially more inflammatory cells than the drug-loaded hydrogel because untreated chronic wounds are said to become trapped in the inflammatory stage of wound healing. Compared to the blank hydrogel, there were more fibroblasts in the drug-loaded hydrogel and commercial dressing. Collagen distribution and organization are crucial factors in evaluating wound healing. While excessive and disordered collagen deposition results in scar enlargement and hinders wound healing, appropriate collagen deposition promotes wound healing. The commercial, blank, and drug-loaded hydrogels produced mature collagen as opposed to the immature and loose collagen seen in the negative control. A granulating layer was seen in both the drug-encapsulated and blank hydrogel groups. The formation of the granulating layer shows that the drug-loaded hydrogel provided antioxidant activity and decreased inflammation, creating a more healing-friendly environment [28-30].

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