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Formulation And Evaluation of Antibacterial Drug Loaded Hydrogel for Wound Healing

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Abstract: *Material And Methods: Hydrogel was prepared from the polymer and various ingredients such as chitosan, polyvinyl pyrolidone, acetic acid, glycerol, sodium hydroxide, Propyl paraben, Methyl paraben. The prepared hydrogel was evaluated for various Physical parameters such as Organoleptic property, pH, Viscosity, Swelling ratio, In vitro drug release, antimicrobial test and stability study.*
Result: The formulations were found homogenous, easily spreadable. The formulated hydrogel is compatible with normal physiology.
Conclusion: The present investigation was found that the formulated hydrogel was found to be more efficient and suitable for wound healing. This formulated hydrogel contains the chitosan and antibacterial drug and other ingreadients they show beneficial action on skin.

Keywords: Hydrogel, wound healing, Antibacterial drug loaded

I. INTRODUCTION

Wound healing, a fundamental physiological process involving the intricate interplay of various cell types, growth factors, and cytokines, aims to restore tissue integrity following injury. While acute wounds typically progress through this process rapidly without extensive intervention, chronic wounds, such as burn wounds, diabetic ulcers, and pressure ulcers, present a significant clinical challenge, often characterized by prolonged healing times and increased susceptibility to infection. Despite advancements in medical technology, effective management of chronic wounds, particularly those complicated by bacterial colonization, remains a major concern.

The use of antibacterial agents is a cornerstone in preventing and treating wound infections. However, the escalating threat of antibiotic resistance necessitates the exploration of alternative and more effective antimicrobial strategies. Furthermore, the systemic administration of antibiotics can lead to adverse side effects and disrupt the normal microbial flora. In this context, localized drug delivery systems that can provide sustained and targeted release of antibacterial agents directly to the wound site are highly desirable. Hydrogels, three-dimensional networks of hydrophilic polymers capable of absorbing and retaining substantial amounts of water, have emerged as a promising platform for wound care application. Their inherent biocompatibility, moist wound environment maintenance capabilities, and potential for controlled drug release make them ideal candidates for delivering therapeutic agent. By incorporating antibacterial drugs into hydrogel matrices, it is possible to achieve sustained drug release at the wound site, potentially enhancing therapeutic efficacy, minimizing systemic side effects, and reducing the risk of developing antibiotic resistance.

This research focuses on the **formulation and evaluation of antibacterial drug-loaded hydrogels** for wound healing. We aim to develop a hydrogel-based delivery system capable of providing sustained release of an antibacterial agent, thereby promoting effective wound disinfection and facilitating the natural healing process. This study will investigate the physicochemical properties of the formulated hydrogels, their drug release kinetics, and their antibacterial efficacy in vitro. Ultimately, this work seeks to contribute to the development of advanced wound care dressings that can effectively address the challenges associated with wound infections and promote efficient healing.

Advantages:

- Targeted Treatment**:** Hydrogels put the medicine right where it's needed in the wound, so the rest of your body isn't exposed to it as much.

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- Long-Lasting Effect: The hydrogel releases the medicine slowly over time, so it keeps working for longer, and you don't have to change dressings as often
- Less Resistance: By focusing the medicine on the wound, it might help prevent bacteria from becoming resistant to antibiotics.
- Better Healing Conditions**:** Hydrogels keep the wound moist, which helps new skin cells grow and move, leading to faster healing.
- Protective Barrier: The hydrogel acts like a bandage, keeping germs out and protecting the wound from getting bumped.
- Body-Friendly: Many hydrogels are made of materials that don't usually cause irritation or allergic reactions.
- Customizable: Scientists can change how the hydrogel works (how much it swells, how strong it is, how fast it breaks down) to fit different types of wounds and medicines.
- More Than Just Antibiotics**:** You can even put other helpful things in the hydrogel, like substances that reduce swelling or help skin grow.
- Easier for Patients: Fewer dressing changes mean it's more convenient and comfortable for people.
- Could Save Money: In the long run, fewer dressing changes and less need for strong antibiotics might make treatment cheaper.

Table No.1 List of materials

Sr.No.	Materials
1	Doxycycline
2	Chitosan
3	Poly vinyl pyrolidone
4	Acetic acid
5	Glycerol
6	Sodium hydroxide
7	Disodium phosphate
8	Monopotassium phosphate
9	Methyl parabean
10	Propyl parabean
11	Tea tree oil
12	Lavender oil
13	Sodium chloride

Hydrogels: They are three-dimensional networks made of water-loving polymers that can absorb and hold a lot of water. Hydrogels have become a promising way to deliver antibacterial drugs to wounds. This is because they can release the drug slowly, help the wound heal, and potentially reduce the chance of bacteria becoming resistant to the drug. Hydrogels can be made from different types of polymers, including natural ones like collagen, gelatin, and chitosan, and synthetic ones like polyethylene glycol and polyvinylpyrrolidone. The characteristics of hydrogels, such as how much they swell, how strong they are, and how quickly they break down, can be adjusted for specific uses.

Sustained Drug Delivery: To release antibacterial agents over a longer period at the wound site.

Promote Wound Healing: To create a moist environment beneficial for tissue repair.

Reduce Antibiotic Resistance: To deliver drugs locally and maintain effective concentrations, potentially lowering the risk of resistance.

Antibacterial Agents Used:

A variety of antibacterial agents are being explored for wound healing, including antibiotics, antiseptics, and antimicrobial peptides. However, antibiotic resistance and side effects are concerns. Hydrogels offer advantages for delivering these agents by providing sustained release and reducing resistance risks.

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Formulation of Hydrogels:

Creating hydrogels for wound healing involves:

1.Polymer Selection: Choosing the right polymer or combination of polymers.

2.Hydrogel Preparation: Forming the three-dimensional network.

3.Antibacterial Agent Incorporation: Adding the drug into the hydrogel matrix

EXPERIMENTAL WORK

Objectives

1.Select an appropriate antibacterial drug for wound healing applications.

2.Develop a chitosan-based hydrogel formulation incorporating the selected antibacterial drug using a suitable method.

3.Conduct comprehensive physicochemical characterization and evaluation to optimize the hydrogel formulation.

Methodology

The research will be conducted in three main parts: Preformulation Studies, Optimization of Hydrogel Formulation using Quality by Design (QbD), and Stability Study.

Part A: Preformulation Studies

This stage will focus on characterizing the selected antibacterial drug to gain essential information for formulation development. The following studies will be performed:

Melting Point Determination: To assess the thermal characteristics and purity of the drug.

Solubility Study: To determine the solubility of the drug in various solvents, which is crucial for selecting the appropriate formulation method and release medium.

Spectral Analysis:

λmax Determination: To identify the wavelength of maximum absorbance for the drug using UV-Vis spectroscopy.

Plotting of Calibration Curve: To establish a quantitative relationship between drug concentration and absorbance for subsequent drug analysis.

Drug-Polymer Compatibility Studies:

Fourier Transform Infrared (FTIR) Spectroscopy: To investigate potential interactions between the drug, chitosan polymer, and their physical mixture by analyzing their characteristic functional groups.

Differential Scanning Calorimetry (DSC): To further assess drug-polymer compatibility by examining thermal transitions and potential changes in the drug's or polymer's thermal behavior in the mixture.

Part B: Optimization of Prepared Hydrogel using QbD

This part will involve the formulation and evaluation of the antibacterial drug-loaded chitosan hydrogel, employing a Quality by Design (QbD) approach to optimize the formulation parameters.

1. Loading of Antibacterial Drug into Hydrogel: The selected antibacterial drug will be incorporated into the chitosan hydrogel matrix using an appropriate method. The specific method will be determined based on the drug's physicochemical properties and the desired release profile.

2. Evaluation of Prepared Hydrogel: The formulated hydrogels will be subjected to the following evaluations:

Organoleptic Properties: Assessment of macroscopic characteristics such as appearance, color, and texture.

pH of Hydrogel: Measurement of the hydrogel's pH to ensure compatibility with skin.

Swelling Ratio of Hydrogel: Determination of the hydrogel's ability to absorb and retain water, which is crucial for maintaining a moist wound environment and drug release.

In vitro Drug Release: Evaluation of the rate and extent of drug release from the hydrogel matrix under simulated physiological conditions.

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Antimicrobial Test: Assessment of the hydrogel's efficacy in inhibiting the growth of relevant wound pathogens using in vitro microbiological assays.

Part C: Stability Study

The optimized hydrogel formulation will undergo stability studies under various storage conditions (e.g., different temperatures and humidity levels) for a predetermined period. This will assess the long-term physical, chemical, and microbiological stability of the hydrogel and the drug within the matrix.

METHOD OF PREPARATION OF HYDROGEL

The required amount of chitosan polymer was dissolved in acetic acid using mechanical stirrer.
Dissolve PVP in water under using mechanical stirrer.
Dissolve doxycycline in water using mechanical stirrer.
Combine chitosan and PVP solution, then add doxycycline solution.
Adjust pH using 0.1 N NaoH.
Add glycerol, methyl paraben, and propyl paraben.
Mix lavender oil and tea tree oil then add to the formulation and stir until homogenous formulation obtained using mechanical stirrer

II. RESULT AND DISCUSSION

Doxycycline in situ gels

Pre-formulation studies

Melting point

Using capillary method, melting point of doxycycline was determined as 172ºC.

Solubility study

Doxycycline is soluble in water and also soluble in aqueous HCL acid.

Ultraviolet-Visible (UV-Visible) Spectroscopy

A.Determination of λmax of Doxycycline

The λmax of Doxycycline hydrochloride showed at 273 nm which was in well compliance with the λmax value of Doxycycline quoted in the literature. The spectrum traced using UV-spectrophotometer.

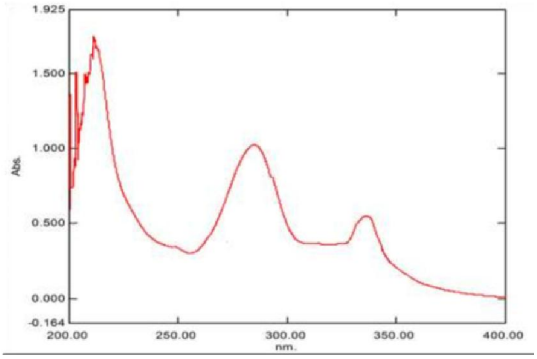

Fig. 1: UV Spectrum of Doxycycline

Standard plot

The values and calculations are depicted in the table 2 and fig. 2 respectively

Concentration (mcg/ml)	Absorbance (273 nm)
0	0.00
5	0.162
10	0.297

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15	0.439
20	0.582
25	0.729
30	0.848

Table. 2: Calibration value of Doxycycline

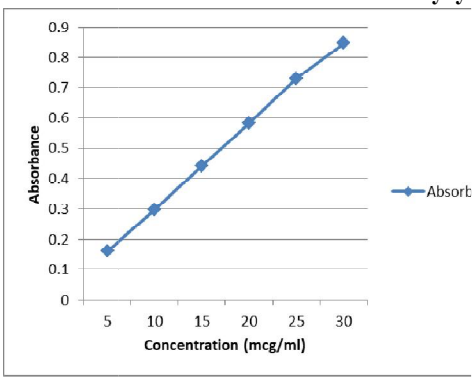

Fig. 2 : Calibration curve of Doxycycline

FT-IR Spectrum

Comparisons of spectra of of pure Doxycyline, along with the physical mixture shows the absence of interaction and presence of drug in unchanged form. FT-IR spectra data are presented in Table 3.

Table. 3 : FT-IR frequencies of pure drug and physical mixture

Functional Group	Reported Frequencies (in cm^{-1})	Frequencies in the Pure Drug (in cm^{-1})	Frequency in the physical mixture (in cm^{-1})
N-H Stretching vibrations	3260	3268	3281
CH_3 Stretching vibrations Aromatic CH Stretching vibrations	2400-3000	2764	2770
C=O Stretching vibrations of residual	1680	1689	1692
N-H Bending vibrations and C=O ring stretching	1601	1557	1550
CH_3 Bending vibrations	1459	1459	1470
O-H and C-H Stretching vibrations	1324	1324	1335
C-O and C-OH Bending vibrations	1234	1245	1252
C-N Stretching vibrations	1230-1320	1320	1328
Aromatic C-H Bending vibrations	666-997	865	871

Fig. 4: DSC of a. pure drug and b. physical mixture

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Evaluation of Doxycycline in situ gel

Organoleptic properties

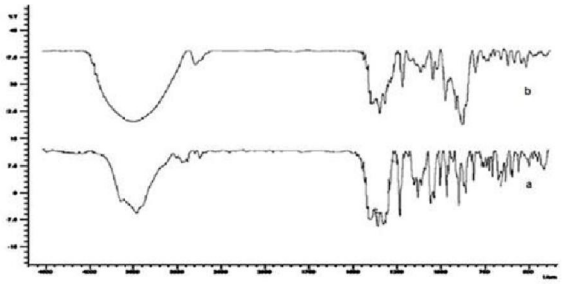
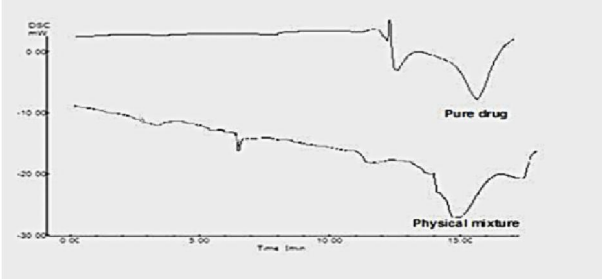


Fig. 3: FT-IR spectra of a. pure drug and b. physical mixture

Differential Scanning Calorimetry Analysis

DSC data are presented in Fig. 4. Doxycycline hydrochloride's thermogram curve showed an endothermic sharp peak at 168.5°C due to semicrystalline doxycycline melting temperature. The DSC curve of physical mixture showed the presence at 171.7°C of endothermic peaks corresponding to doxycycline melting. Comparisons of pure Doxycyline endothermic peaks along with the physical blend show the lack of drug interaction and drug presence in unchanged



The formulation was much clear and transparent with good homogeneity and absence of lumps.

pH of hydrogel

Formulations prepared had a pH in the range of 4.40 – 4.45, which is then adjusted using 0.1 N NaOH to 5.5– 5.8 to avoid discomfort on application to the skin.

Viscosity

Viscosity of optimized formulation at 37°C was 23400 cps.

Swelling Ratio Study of Hydrogel

It was observed in situ gel formulation show the swelling ratio of 86.05 %.

In vitro drug release studies

It was found that drug release was 58% after 12 hr for formulation.These can be due to the higher concentration of chitosan and PVP. The in vitro release studies data is presented in Table no.4

Table. 4: In vitro drug release data

Time (h)	Absorbance	Sampled Concentration (µg/mL)	Amount Released in Sample (mg)	Cumulative Amount Released (mg)	Cumulative Release (%)
2	0.224	8	0.4	0.4	4
4	0.36	13	0.65	1.05	10.5
6	0.481	17	0.85	1.9	19
8	0.616	22	1.1	3	30
10	0.736	26	1.3	4.3	43
12	0.865	30	1.5	5.8	58

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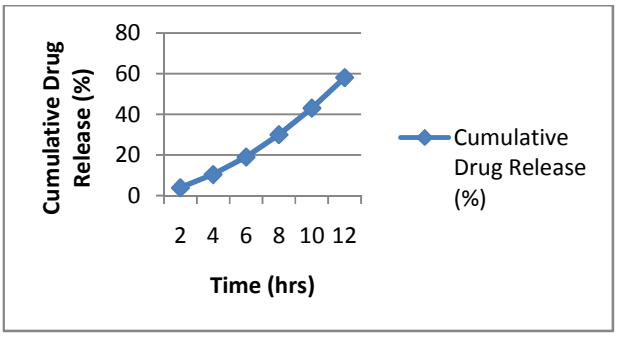

Fig. 5: Result of in vitro drug release studies

Antimicrobial Test for Antibacterial Drug Loaded Hydrogel

Disk	Sample	Zone of Inhibition Diameter (mm)	Interpretation
A	Doxycycline-loaded hydrogel extract	25 mm	Significant antibacterial activity
B	Control hydrogel extract (no drug)	0 mm	No antibacterial activity observed
C	Standard Doxycycline solution (10 µg/mL)	30 mm	Expected antibacterial activity

Table. 5: Antimicrobial test result for antimicrobial drug loaded hydrogel

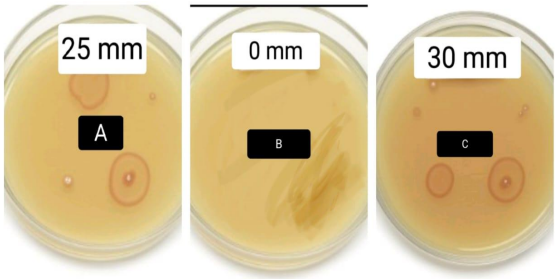

Fig. 6: Result of in vitro drug release studies

Stability Studies

As the developed hydrogel is supposed to be stored at refrigerated temperature, 5±3°C temperature condition was implied for assessing long term storage. No significant change in the physical properties and drug content of the formulation was perceived during the study period, exhibiting good stability.

Storage condition	Sampling interval (months)	Physical appearance	%Drug Content
5±3°C	0	Transparent, No precipitation	38%
	1	Transparent, No precipitation	37%
	2	Transparent, No precipitation	36%
	3	Transparent, No precipitation	34%
25±2°C/	0	Transparent, No precipitation	38%

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60±5% RH	1	Transparent, No precipitation	37%
	2	Transparent, No precipitation	36%
	3	Transparent, No precipitation	33%

Table. 6 : Optimized hydrogel stability studies data

III. SUMMARY AND CONCLUSION

SUMMARY

The study's objective was to formulate antibacterial drug loaded hydrogel and to evaluate it. The drugs used in the research are doxycycline. In vitro studies assessed the formulated hydrogel. The work consisted of different studies, the important results of which are summarized below.

FT-IR and DSC spectra's showed no compatibility issues between the drug and physical formulation. The visual appearance of the formulations was acceptable. The pH of the formulation was in the range of 4.40 - 4.45 and adjusted to skin pH using NaoH to avoid irritation. The viscosity of formulation at body temperature was found to be 23400 cps.The drug content of formulation was in the acceptable range. It was found that the formulation showed drug release for 12 hr and showed controlled release of the drug.

No appearance of turbidity which indicated no microbial growth in formulation. From the stability studies, it was confirmed that no significant change in the physical properties and drug content of the optimized formulation.

CONCLUSION

The advanced formulations comprising chitosan were found to act on each element of the wound restoration process. It allows the healing method to continue in an organized and timely manner without interruption at any stage in the stages of the wound.Thus, formulations comprising of chitosan with antimicrobial agent will certainly demonstrate to be efficient wound healing agents in treating wounds. The above formulation showed good physical properties, drug content, in vitro drug release and stability which is evident from above studies.

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