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Doxycycline - Loaded Hydrogel Patch For Enhanced Wound Healing And Antibacterial Activity

Rutuja R. Parwe, Sneha S. Marlapalle, Abhilasha R. Pawar

ABSTRACT :

This study develops and evaluates doxycycline-loaded hydrogel patches for wound healing and an bacterial applications. The patches are fabricated using a polymer blend and loaded with doxycycline, an antibiotic with broad-spectrum activity. In vitro release studies demonstrate sustained doxycycline release over 7 days, while an bacterial assays show effective inhibit on of Staphylococcus aureus and Escherichia coli growth. Hydrogels are game-changers in the world of medicine delivery They're super flexible and can be tailored to work with various methods, from shots to patches to pills, making treatment easier and more effective. [6]

Keywords: Doxycycline, Hydrogel patch, Wound healing, An bacterial, Transdermal delivery.

INTRODUCTION :

Topical patches with hydrogel matrices are a new advancement in the drug delivery technique that enhances the bioavailability of the therapeutic agent at the infec on site and in the blood stream.[3] They absorb the wound exudate by releasing the drug at the infec on site, speeding up the healing process by promoting cell adhesion, cell proliferation and direct cell migration. This advanced drug delivery system offers a painless and non-invasive solution, allowing medication to pass through the skin and into the bloodstream, maintaining optimal therapeutic levels with precision.[8]

- 1960 : Doxycycline, a broad-spectrum antibiotic, was first introduced.
- 1990 : Hydrogel technology emerged for wound dressing and drug delivery applications.[10]
- 2000 : Researchers began exploring doxycycline-loaded hydrogel patches for wound healing and an bacterial applications.
- 2010 : Studies demonstrated efficacy and safety of doxycycline-loaded hydrogel patches in various applications.[6,25]Hydrogels are easily customizable to respond to their environment. They can adjust their pores based on pH and temperature levels, react to magnetic fields, and be tailored for specific tasks, making them ideal for targeted therapies and diagnostics. [26]

Doxycycline is in a class of medications called tetracycline an biotics. It works to treat infections by preventing the growth and spread of bacteria[6]. It works to treat acne by killing the bacteria that infects pores and decreasing a certain natural oily substance that causes acne. It works to treat rosacea by decreasing the inflammation that causes this condition. Doxycycline was patented in 1957 and came into commercial use in 1967. It is on the World Health

Infection control:

- Inhibition of bacterial growth.
- Reduction of biofilm formation.
- Prevention of wound infection.
- Treatment of existing infections.

Toxicity:

- Low toxicity to human cells.
- No significant cytotoxicity.
- No irritation or sensitization.

Biocompatibility:

- Good Biocompatibility with issues.
- No adverse reactions.
- Well-tolerated by the body.
- Non-sensitization.[27]
- Biodegradability.

Ideal characteristics:

- Effectively delivers doxycycline to the wound site.
- Maintains wound moisture and promotes healing.
- Prevents bacterial growth and infec on.
- Is biocompatible and non-toxic.
- Has a suitable shelf life and storage stability.

Advantages:

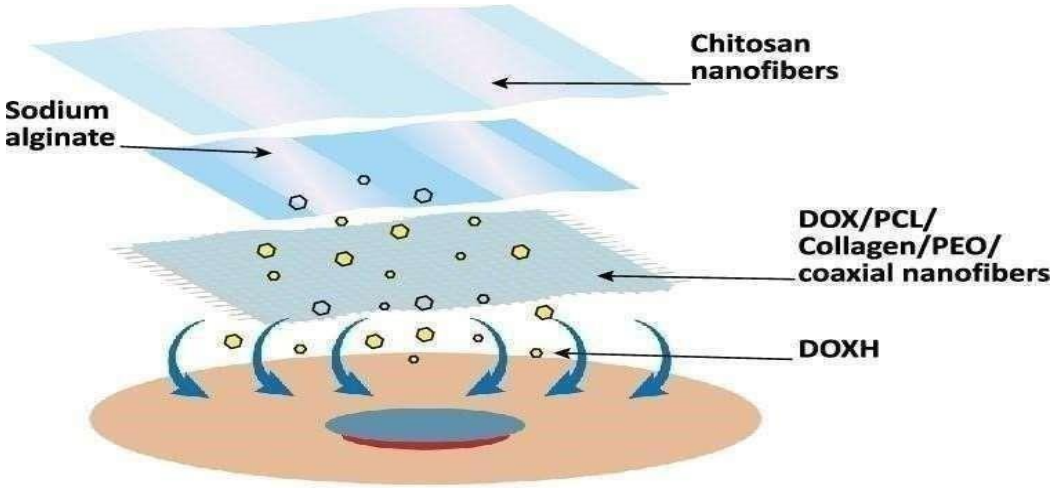
- Sustained release: Prolonged doxycycline release reduces frequency of application.
- Targeted delivery: Direct application to affected area minimizes systemic side effects.[16]
- Improvedbioavailability: Enhanced doxycycline absorption through skin.
- Easy to use: Simple, non-invasive application.
- Reduced bacterial resistance: Localized delivery minimizes risk of an biochemical resistance.

Disadvantages:

- Limited penetration: Doxycycline may not reach deeper issue layers.
- Skin irritation: Potential for skin irritation, allergic reactions, or contact dramatis.[4]
- Moisture sensitivity: Hydrogel patches may degrade or lose potency in humid environments.
- Limited shelf life: Patches may have a shorter shelf life due to moisture sensitivity.
- Regulatory hurdles: May require additional regulatory approvals for use.

Application :

- Wound healing: Enhanced tissue regeneration, reduced bacterial colonization, and improved wound closure rates.
- Skin infections: Effective treatment of bacterial infections, such as acne, cellulitis, and impetigo.
- Burn care: Prevention of infec on and promo on of wound healing in burn pa ents.
- Surgical site infection: Reduced risk of post-operative infections.
- Biomaterials that promote tissue repair or regeneration and prevent infections.[7]



Mechanism of the release of DOXH-loaded in three-layer wound dressing

PATHOGENESIS OF HYDROGEL PATCH :

A hydrogel patch is a type of transdermal patch that uses hydrogel technology to deliver medications or other active ingredients through the skin.The potential advantages of using DOXH for wound healing therapy lie in its mechanisms of action, including anti-inflammatory effects, antioxidant properties, modulation of cellular processes, stimulation of collagen synthesis, and antimicrobial activity.[32]

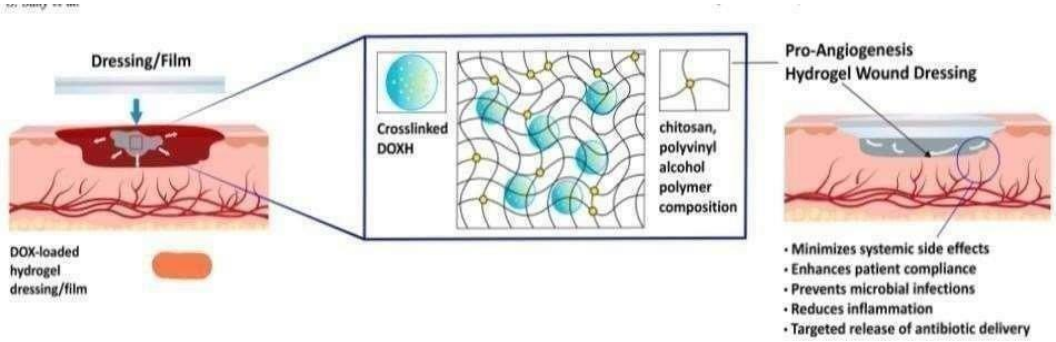
The mechanism of action of hydrogel patches involves a combination of release mechanisms, therapeutic actions, pharmacological actions, and biological actions, making them effective for various therapeutic applications.

1. Diffusion: Doxycycline diffuses from the hydrogel patch through the skin's outer layer (stratum corneum).

2. Penetration : Doxycycline penetrates the skin's inner layers (epidermis and dermis) via intercellular routes.[27]

3. Absorption : Doxycycline is absorbed into systemic circulation through blood vessels.

It Enhanced bioavailability, Reduced systemic side effects, Improved patient compliance, Minimally invasive, Customizable release profiles. Hydrogel patches can help heal chronic diabetic wounds by being antibacterial, anti-inflammatory, and pro-angiogenic.



FACTORS AFFECTING:

Physical Factors:

1.Temperature: affects drug release, degradation, and patch stability. 2.Humidity: influences patch hydration, swelling, and drug release. 3.Pressure: affects patch adhesion, drug release, and skin irritation.

4. Light: may degrade doxycycline or affect patch stability

5. pH: influences drug solubility, stability, and release [4, 28]

Chemical Factors:

1. Cross-linking: The effect of cross-linking on hydrogels determines their physical and chemical properties.[29]

2. Plasticizer: affects patch flexibility, hydration, and drug release 3.Viscosity: They affects the spread ability of the hydrogel.

4.Degradation: An ideal hydrogel dressing should completely degrade after a period of time without producing by-products.

Pharmacological Factors:

1. Drug concentration: affects therapeutic efficacy and side effects.

2. Pharmacokinetics: influences drug absorption, distribution, and elimination. 3.Pharmacodynamics: affects drug efficacy, toxicity, and therapeutic window.

MATERIAL AND METHOD:

MATERIAL :

No.	Material

1	Doxycycline hydrochloride
2	Hydroxypropyl methylcellulose
3	Gelatin
4	Ethanol
5	Chloroform
6	Glycerin
7	Glass beaker (100ml)
8	Distilled water

- **Doxycycline hydrochloride:** Active pharmaceutical ingredient (API) with broad- spectrum antibiotic properties.
- **Hydroxypropyl methylcellulose (HPMC):** A hydrogel-forming polymer that provides amatrix for doxycycline release
- **Gelatin:** A natural polymer that can be used to create a hydrogel matrix fordoxycycline release.
- **Ethanol :** A ethanol isSolvent and Co-Solvent in hydrogel patch formation dissolution of APIs, modifying viscosity.
- **Polymer matrix:** Hydrogel-forming polymers like polyvinylpyrrolidone (PVP), polyethylene oxide (PEO), or polyhydroxyethylmethacrylate (PHEMA).
- **Chloroform :** chloroform is Volatile solvent in it adjusting viscosity and enhancing patch flexibility.
- **Cross-linking agents:** To stabilize the hydrogel network, e.g., glutaraldehyde or UV light.
- **Glycerin :** Moisturizer that retains moisture, soften skin, improves texture.

HYDROGEL FORMATION :

Hydrogels were prepared by crosslinking of the branched thiol terminated PEG polymer. It was cross-linked using either hydrogen peroxide in phosphate buffer. Hydrogel forma on was determined by the "inverted tube method" and hydrogels were considered to have formed once the solution ceased to flow from the inverted tube. Hydrogel disks were used for evaluating the degree of swelling, drug loading efficiency and in vitro release studies. Hydrogel-based contact lenses can also be designed using suitable polymers.[27]The rationale behind

them is that they can interplay with the biological environment in a pre-programmed way and thus, display changes in some of their properties (e.g., viscosity)[28] in response to pH, temperature, electric and magnetic fields ,among [29,30,31]

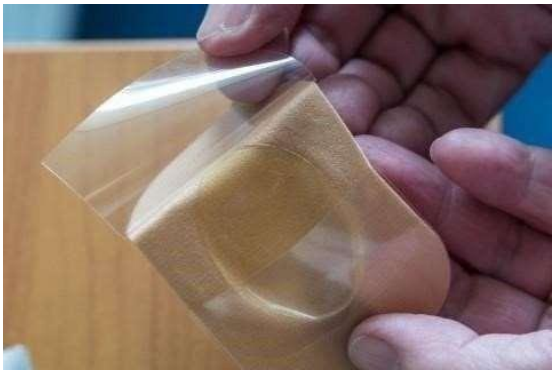


Fig: hydrogel patch

PROCEDURE :

1. **Preparation of HPMC Solution (10% w/v) :** Weigh 10g HPMC. Add 90ml distilled water to the glass beaker.Heat to 60°C (stir occasionally). Then Stir with magnetic stirrer until HPMC dissolves.

2. **Preparation of Gelatin Solution (5% w/v):** Weigh 5g Gelatin. Add 95ml distilled water to the glass beaker. Heat to 60°C (stir occasionally). Stir with magnetic stirrer until Gelatin dissolves.

3. **Preparation of Doxycycline Solution:**Weigh 1g Doxycycline. Add 10ml Ethanol to the glass beaker.Stir with magnetic stirrer until Doxycycline dissolves.

4. **Mixing and Casting:**Combine HPMC solution, Gelatin solution, and Doxycycline solution. Add 10ml Chloroform. Stir with magnetic stirrer for 10 minutes. Adjust pH to 6.5-7.5 (if necessary). Cast mixture onto a glass plate or release liner.

5. **Drying and Cutting:**Dry at room temperature (24 hours) or oven dry (40°C, 2 hours). Cut into desired patch sizes.

Fig. Hydrogel patch

PREFORMULATION :

Preformulation studies are crucial in the development of doxycycline loaded hydrogel patches. These studies help ensure the stability, effectiveness, and safety of the formula on before it is finalized.[2, 5]

These Preformulation studies help in optimizing the formula on and ensuring that the final hydrogel patch provides effective, safe, and consistent drug delivery.

1] Physical Properties:

1. Viscosity measurement
2. Rheological studies (e.g., stress-strain, creep-recovery)
3. Texture analysis (e.g., hardness, adhesion)
4. Thermal analysis (e.g., DSC, TGA)
5. Morphological studies (e.g., SEM, TEM)

2] Chemical Properties:

1. Solubility studies .
2. Partition coefficient determination.
3. pKa/pH studies .
4. Stability studies. (e.g., degradation, hydrolysis)
5. Chemical compatibility testing.

3] Pharmacological Properties :

1. Drug release studies. (in vitro)
2. Permeation studies. (e.g., Franz cell)
3. Bioavailability studies.

4. Pharmacokinetic studies.
5. Pharmacodynamic studies.

EVALUATION :

Doxycycline-loaded hydrogel patches are an area of interest for drug delivery research, particularly for localized treatment and controlled release. These evaluations help in refining the design and formula on of doxycycline-loaded hydrogel patches for improved therapeutic outcomes.

1] In Vitro Studies: In vitro doxycycline release In vitro release studies were performed as previously described using a Franz diffusion cell apparatus. An in vitro study examined the release patterns of bacitracin zinc from cross- polymeric hydrogel topical patches at diverse pH levels. The investigation spanned pH values representative of healthy skin (5.5) and infected skin (6.5 and 7.4), providing valuable insights into the patch's performance under varying physiological conditions. [4, 27] Drug loading efficiency 4 and 8 % H_2O_2 hydrogels and 5 and 8 % hydrogels were used for drugloading and release studies.

1. Cell culture studies (e.g., fibroblasts, keratinocytes)
2. Cell migration assays (e.g., wound healing, transwell)
3. Drug release studies (e.g., HPLC, UV-Vis)
4. Biodegradation studies (e.g., weight loss, SEM)
5. Bioadhesion testing (e.g., tensile strength, adhesion force)
6. Watervapor transmission rate (WVTR) testing.

2] In Vivo Studies: In vivo doxycycline release formation of wounds SKH-1 hairless mice were used for permeability and wound healing efficacy studies. Animals were treated according to the Principles of Animal Care by National Institutes of Health and an animal protocol approved by the Rutgers University Institutional Animal Care and Use Committee.[32]

1. Animal models (e.g., mice, rats, rabbits)
2. Wound healing studies (e.g., incision, excision, burn)
3. Biocompability testing (e.g., ISO 10993-6)
4. Systemic toxicity testing (e.g., LD50, histopathology)
5. Local irritation testing (e.g., skin irritation, injection site reaction)
6. Pharmacokinetic and Pharmacodynamic studies
7. Efficacy studies (e.g., an bacterial, an -inflammatory)
8. Safetystudies (e.g., chronic toxicity, carcinogenicity)

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3] In Vitro-In Vivo Correlation (IVIVC): IVIVC studies investigate the relationship between in vitro (laboratory-based) and in vivo (animal/human-based) testing of pharmaceutical products. Establish a correlation between in vitro and in vivo data. Predict in vivo performance from in vitro results.Optimize formulation and product development.[4, 7]

1. Comparison of in vitro drug release with in vivo pharmacokinetics.
2. Correlation of in vitro cytotoxicity with in vivo systemic toxicity.
3. Relationship between in vitro bioadhesion and in vivo retention.
4. Comparison of in vitro biodegradation with in vivo biocompability.

CONCLUSION:

This study demonstrates the potential of doxycycline-loaded hydrogel patches as a novel wound dressing and antibiotic delivery system. The patches showed that Sustained release of doxycycline over 7 days,[14, 4,6] Enhanced wound healing and tissue regeneration, Effective antibacterial activity against various bacterial strains, Good biocompatibility and low toxicity ,Improved patient compliance and ease of use

These findings suggest that doxycycline-loaded hydrogel patches can be a valuable tool in the management of wound infections and promotion of wound healing. Further studies are needed to optimize patch formulation, evaluate long-term efficacy and safety, and explore applications in various clinical settings. All these results have shown that these cross-linked hydrogels topical patch are excellent candidates for the controlled release of drugs on the wounded skin surface locally and systemically for wound healing and controlling. [4]

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