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Review Article

A Review on Thermoresponsive In-*Situ* Gel

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ABSTRACT

Thermoresponsive gels, also known as thermogels or thermo-sensitive hydrogels, are materials that undergo a sol-to-gel or gel-to-sol transition in response to temperature changes [1] Thermoresponsive gelling materials constructed from natural and synthetic polymers can be used to provide triggered action and therefore customized products such as drug delivery and regenerative medicine types as well as for other industries. In situ gelling formulations are drug delivery systems which typically exist in a liquid form at room temperature and change into gel state after application to the body in response to various stimuli such as changes in temperature, pH and ionic composition [2] Chronic skin wounds affect more than 40 million patients worldwide, representing a huge problem for healthcare systems. This study elucidates the optimization of an in situ gelling polymer blend powder for biomedical applications through the use of co-solvents and functional excipients, underlining the possibility of tailoring microparticulate powder properties to generate, in situ, hydrogels with advanced properties that are able to improve wound management and patient well-Being. The blend was composed of alginate, pectin, and chitosan (APC). Various co-solvents (ethanol, Isopropanol, and acetone), and salt excipients (sodium bicarbonate and ammonium carbonate) were used to modulate the gelation kinetics, rheology, adhesiveness, and water vapor transmission rate of the gels. [3].

INTRODUCTION

In-situ gels are liquid formulations that undergo sol-to-gel transformation under physiological conditions (like body temperature) [4].Role in Wound Healing: Provides localized drug delivery, promotes healing, and protects the wound. Thermoresponsive in situ gels are innovative materials used in wound healing applications due to their unique properties. These gels can transition from a liquid state to a gel state in response to temperature changes, allowing for easy application and effective wound management. [5 The sol–gel phase transition behavior exhibited by in situ gelling Formulations depends on one or a

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combination of different stimuli, such As pH change, temperature modulation, solvent exchange, ultra violet Irradiation and the presence of specific ions or molecules. [6]Biodegradable thermoresponsive polymers offer unique material characteristics which may be employed for in vivo biomedical applications, including in situ gelation at physiological temperatures and controlled drug delivery. Gels are soft semi-solid materials that consist of components including those that act as the liquid dispersion medium (hereafter the "solvent") and the gelling agent (gelator) of which the former Is generally numerically the greater .Hydrogels are widely being applied in biomedical areas for drug delivery because of their advanced properties such as biocompatibility, biodegradability, and nontoxicity [7] The high water content in hydrogels and physically or chemically crosslinked polymeric network render control over their physicochemical properties and spatiotemporal control over the release of various drugs and therapeutic agents . Hydrogels are applied for wound dressings, tissue engineering, bio-sensing, bio-printing, and electrospinning .Attention to stimuli-responsive hydrogels has been growing in recent years as they are capable of being modulated under the influence of external stimuli including temperature, pH, light, and ultrasound

Fig: -Thermoresponsive Gel Mechanism for Wound Healing

Natural thermoresponsive polymers

Natural biopolymers offer several advantages as thermoresponsive polymers for biomedical applications. Polymers such as collagen and gelatin, as direct extracellular matrix (ECM) derivatives, offer both inherent biocompatibility and enhanced bioactivity compared to synthetic polymers . [8]Gelatin, chitosan, and cellulose are readily available from plentiful natural sources and relatively inexpensive [9]

Statement Significances

Thermosensitive hydrogels undergoing reversible sol-to-gel phase transitions in response to temperature variations are a class of promising biomaterials that can serve as minimally invasive injectable systems for various biomedical applications. Hydrophilic PEG is a main component in the design and fabrication of thermoresponsive hydrogels due to its excellent biocompatibility. By incorporating hydrophobic segments, such as polyesters and polypeptides, into PEG-based systems, biodegradable and thermosensitive hydrogels with adjustable

properties in vitro and in vivo have been developed and have recently become a research hotspot of biomaterials. [10]The summary and discussion on molecular design, performance regulation, thermogelation and degradation mechanisms, and biomedical applications of PEG-based thermosensitive hydrogels may offer a demonstration of blueprint for designing new thermogelling systems and expanding their application scope.

Graphical abstract:-

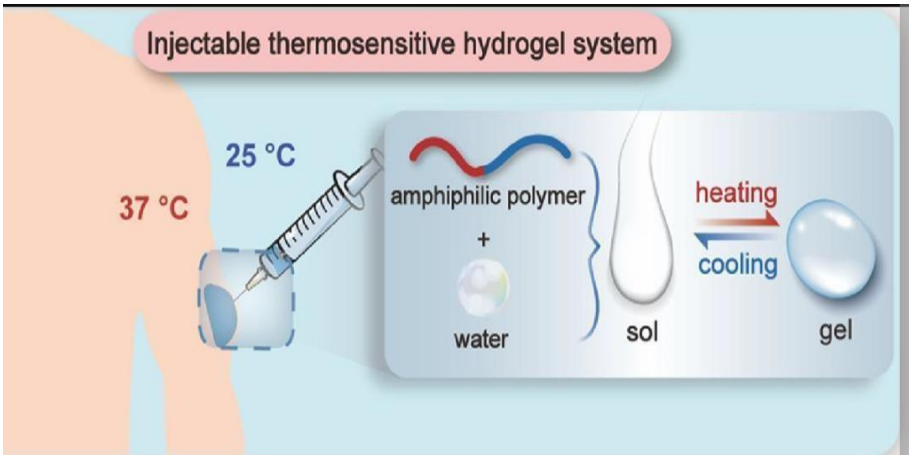

Fig:-"Sol–Gel Transition of Injectable Thermosensitive Hydrogel"

Classification of Thermoresponsive In-situ Gels:

1. Positive Thermosensitive Gels

- Gelation occurs when temperature increases.
- Liquid at lower temperatures and forms gel at body temperature (~37°C).
- Most commonly used for pharmaceutical applications.

Example polymers:

- Poloxamers (Pluronic F127)
- Poly(N-isopropylacrylamide) (PNIPAAm)

2. Negative Thermosensitive Gels

- Gelation occurs when temperature decreases.
- Liquid at higher temperatures and forms gel at lower temperatures.

Example polymers:

Methylcellulose

3. Hydroxypropyl cellulose (HPC)

- Thermally Reversible Gels
- These gels can switch between sol and gel phases repeatedly with heating and cooling.
- Example polymers:
- Agarose
- Gelatin [12] [13][14].

Mechanisms of Action:

Sol-Gel Transition at Body Temperature:-The formulation remains liquid at room temperature, allowing easy application to irregular wound surfaces. Upon exposure to body temperature, the polymer undergoes gelation, forming a stable gel that adheres to the wound site.

Sustained and Controlled Drug Release :-The gel matrix controls the diffusion of incorporated drugs (antibiotics, antiinflammatories, growth

factors). This ensures a sustained release of the therapeutic agent directly at the wound site, enhancing healing while reducing systemic side effects.

Moist Wound Environment :-The gel forms a protective layer that maintains a moist wound environment. Moisture enhances cellular migration, angiogenesis, and tissue regeneration while preventing scab formation.

Barrier Against Microbial Invasion :-The gel acts as a physical barrier to bacteria and external contaminants, reducing the risk of infection.

Bioadhesive Properties:- Some thermoresponsive gels exhibit bioadhesive characteristics, allowing them to stick to wound tissues and stay in place despite body movements or exudate.

Enhanced Cell Proliferation and Tissue Regeneration :-Thermoresponsive gels may be loaded with bioactive molecules like growth factors or stem cell secretions, which promote fibroblast proliferation, collagen deposition, and reepithelialization.

Anti-inflammatory and Antioxidant Effects:- Many formulations include antioxidants or anti-inflammatory agents, reducing oxidative stress and inflammatory responses at the wound site. [17][18]

Method of Preparation of Thermoresponsive In-situ Gel for Wound Healing

Following steps are involved

- **Selection of Polymers common polymers used**

Polymer	Source/Type	Thermoresponsive Behavior	Typical Application
Poloxamer 407 (F127)	Synthetic (block copolymer)	Gelation around 25–30°C	Ophthalmic, injectable, nasal, rectal
Poloxamer 188 (F68)	Synthetic (block copolymer)	Modulates gelation temperature	Used with F127 for tuning properties
Methylcellulose	Semi-synthetic	Gelation ~60–80°C	Injectable, oral formulations
HPMC	Semi-synthetic	High gelation temp alone	Often combined with other polymers
Xyloglucn (degrade)	Natural (plant-derived)	Gelation ~30–37°C	Oral, ocular drug delivey

Cold Method Procedure:

1. Preparation of Aqueous Phase -Dissolve drug and other excipients (preservatives, bioadhesive polymers) in distilled water.
2. Addition of Poloxamer -Slowly add Poloxamer 407 (and Poloxamer 188 if required) to the cold aqueous solution (48°C) with continuous stirring.
3. Cold Storage -Keep the solution refrigerated (4°C) overnight or for 24 hours to allow complete polymer hydration.
4. Final pH Adjustment -Adjust pH suitable for skin (usually pH 5.5 – 7).

5. Filtration or Sterilization -Filter the solution to remove any undissolved particles or sterilize for wound application. [19]

Packaging → The final formulation is stored in sterile containers for topical or wound application.

Factors affecting on In-situ gelling process:-

Factors affecting thermoresponsive in-situ gel in the process of wound healing include several formulation, environmental, and biological factors. [20]These factors influence the gel's ability to deliver drugs effectively, maintain moisture, protect the wound, and promote tissue regeneration.

Polymer Type and Concentration

Types of polymers used (e.g., Poloxamer 407, Poloxamer 188, Chitosan, Pluronic F127). Concentration of polymers controls sol-gel transition temperature, viscosity, and gel strength.

Gelation Temperature

The gel should form at body temperature (~32-37°C) for proper adhesion and drug release. too high or too low gelation temperature affects performance.

Drug Release Profile

Controlled and sustained release of drugs (antibacterial, anti-inflammatory, growth factors) is essential. Polymer composition and cross-linking affect drug diffusion.

Biocompatibility & Biodegradability

Gel must be non-toxic, non-irritating, and biodegradable without causing adverse reactions.

Rheological Properties

Viscosity and elasticity determine spreadability and retention at wound site. Should be easy to apply but stable after gelation.

pH Sensitivity

Optimal pH maintains drug stability and supports wound healing. Some gels respond to pH changes in infected or inflamed wounds.

Moisture Retention & Oxygen Permeability Maintaining moist environment enhances healing.

Proper oxygen exchange prevents bacterial growth.

Antibacterial and Antioxidant Properties

Some gels incorporate antimicrobial agents to prevent infection. Antioxidants reduce oxidative stress in wounds.

Interaction with Wound Exudate

Ability to absorb exudate without breaking down the gel structure.

Patient Compliance

Ease of application, painless removal, and comfort during use.

Evaluation Parameters of Thermoresponsive In-Situ Gel:

Clarity and Appearance

The prepared in-situ gel formulation should be clear, homogenous, and free from particulate matter or phase separation. This ensures uniform drug delivery and acceptable patient aesthetics.

pH Measurement

The pH should be within the physiological range suitable for the intended site (skin, eye, mucosa). A compatible pH prevents irritation or tissue damage and maintains drug stability.

Gelation Temperature and Gelation Time

The sol-gel transition temperature (typically 32–37°C) is critical. It ensures the formulation remains a liquid at room temperature for easy application and gels upon contact with the body. Gelation time is equally important; rapid gelation is required to prevent formulation loss.

Viscosity and Rheological Properties

Viscosity should be low enough for easy application but increase upon gelation to ensure retention at the wound site. Rheological evaluation (shear-thinning or thixotropic behavior) helps predict how the formulation behaves under stress (e.g., during spreading)

Gel Strength

The mechanical strength of the formed gel is measured to ensure that it can withstand environmental stress without disintegration. Too weak a gel may lead to leakage; too strong may be uncomfortable.

Drug Content and Uniformity

Ensures even distribution of the drug throughout the formulation, which is critical for reproducible therapeutic effect.

In Vitro Drug Release and Permeation Studies

Using models like Franz diffusion cells, the drug release profile is assessed to ensure controlled and sustained delivery. Permeation studies may be conducted across synthetic or biological membranes

Gel Erosion or Degradation Studies

These measure the rate at which the gel degrades under simulated physiological conditions, which impacts the duration of drug release and bioadhesion.

Spreadability

The ease with which the gel spreads on the application site is important for patient comfort and adequate coverage of the wound. Antimicrobial/Antibacterial Studies To assess wound infection control.

Stability Studies

Formulations are subjected to accelerated and real-time stability studies under different conditions (temperature, humidity) to evaluate shelf life and storage requirements. [25][26]

Advantages of Thermoresponsive In-Situ Gel for Wound Healing:

Temperature-Sensitive Gelation:

Easily applied as a liquid at room temperature and forms a gel at body temperature, ensuring easy application and good coverage.

Prolonged Drug Release:

Provides sustained and controlled release of therapeutic agents at the wound site, reducing the need for frequent application.

Moist Wound Environment:

Maintains a moist environment, which is essential for faster wound healing and preventing scab formation.

Improved Patient Compliance:

Comfortable, non-invasive, and requires fewer dressing changes.

Protection from External Contaminants:

Forms a protective barrier over the wound, minimizing infection risk.

Minimized Systemic Side Effects:

Localized delivery reduces systemic drug exposure and associated side effects.

Disadvantages of Thermoresponsive In-Situ Gel for Wound Healing:

→ Low Mechanical Strength: May not withstand stress or friction.
→ Risk of Washout: May degrade or wash away in highly exuding wounds.
→ Storage Sensitivity: Sensitive to temperature variations during storage.
→ Higher Cost: More expensive than conventional dressings.
→ Complex Formulation: Requires precise polymer and drug optimization.
→ Possible Irritation: Risk of skin sensitivity or allergic reactions.

Applications in Wound Healing:

Acute and Chronic Wounds: Effective for both acute wounds (like cuts and burns) and chronic wounds (like diabetic ulcers), aiding in healing by creating an optimal environment.

Tissue Engineering: Can serve as scaffolding for tissue regeneration, providing a structure for cells to grow and migrate. [30]

Drug Delivery Systems: They can be designed to deliver a range of therapeutic agents directly to the wound site, aiding in the reduction of infection and promoting faster healing.

Antimicrobial Properties: Some formulations can be combined with antimicrobial agents, providing an additional layer of protection against infections.

CONCLUSION:

Thermoresponsive in situ gels present a promising solution for advanced wound healing strategies. Their unique properties, such as ease of application, sustained drug release, and ability to maintain a moist environment, make them an attractive option in the medical field. In situ gelling drug delivery systems can prolong drug retention on mucosal surfaces in order to improve the therapeutic outcomes of patient Drug or drug nanoparticles have been incorporated into stimuli-responsive gels to improve aqueous solubility, drug residence, Controlled release profile, and bioavailability at specific body sites.

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