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A REVIEW ON HYDROGEL DRUG DELIVERY SYSTEMS WITH SPECIAL REFERENCE TO TOBRAMYCIN ANTIMICROBIAL ACTIVITY

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ABSTRACT

Hydrogel-based biomaterials play a significant role in enhancing the effectiveness of skin wound healing applications. This article examines hydrogel instruments designed for biomedical use. This paper begins with a detailed theoretical overview of how hydrogels are synthesized and function. This segment focuses heavily on crosslinking methodologies and operational principles. The second part focuses on hydrogel applications. Hydrogels consist of three-dimensional, cross-linked polymer chains that absorb and trap massive amounts of water in their internal spaces. Practically any water-soluble polymer can form a hydrogel, offering a broad spectrum of chemical compositions and physical properties. Moreover, hydrogels can take multiple physical shapes, including slabs, micro/nanoparticles, coatings, and films. They are often used to deliver tobramycin, an aminoglycoside antibiotic derived from fermenting Micromonospora purpurea or M. echinospora. It consists of a mixture of three main factors: C1, C1a, and C2. Tobramycin is typically formulated as a sulfate salt. Each constituent contains five basic amine groups, necessitating five equivalents of sulfuric acid per mole of the tobramycin free base.

KEYWORDS: Tobramycin, Anti-microbial activity, Hydrogel, Wound healing, *Pseudomonas aeruginosa.*

1. INTRODUCTION

Over the years, the field of wound care has experienced tremendous progress and evolution. This aligns with early observations by the Greek physician Galen (120–201 A.D.), who noted that wounds heal best under moist conditions. Despite early insights, therapeutic strategies for nearly two millenniums prioritized wound desiccation, utilizing highly absorptive gauze pads as the primary modality for clinical management. Although wet-to-dry configurations historically facilitated wound debridement, the contemporary value of traditional gauze dressings is highly controversial. This is primarily because their removal induces significant pain and disrupts the regenerating neo-epithelial layer.[1]

Toward the end of the 20th century, accumulating clinical evidence substantiated these findings, driving the commercial production of occlusive wound care products tailored to sustain and protect an optimal moisture balance during healing. Contemporary occlusive systems expedite tissue re-epithelialization and upregulate collagen biosynthesis. Mechanistically, they establish a temporary hypoxic environment within the wound bed to drive angiogenesis, while concurrently reducing the local pH to create a hostile environment for microbial colonization, thereby lowering clinical infection rates.[2,3] Compared to conventional gauze, these systems demonstrate superior clinical efficacy regarding patient tolerance, logistical convenience, and therapy compliance. Furthermore, they optimize cosmetic recovery by mitigating scar tissue development.[4,5] The primary objective of contemporary wound care systems is the purposeful manipulation of the localized tissue environment to optimize therapeutic pathways. The extensive proliferation of commercial dressing options currently presents a significant selection dilemma when identifying the optimal therapeutic matrix for a given wound type.

Hydrogel matrices represent pivotal biomaterial frameworks engineered to optimize the physiological efficiency of dermal wound regeneration. Representing 10% of the aggregate body mass and expanding across a surface area of roughly two square meters, the cutaneous system is critical for physiological homeostasis, metabolic regulation, and anatomical protection. The cutaneous layer serves as the fundamental immunological barrier restricting pathogen entry. Additionally, it safeguards systemic homeostasis against thermal and barometric shifts via somatosensory signaling to the central nervous system, prompting regulatory neuromuscular actions.[6] The cutaneous layer mediates systemic thermoregulation via perspiration. Morphologically, the skin is categorized into three primary cellular strata:

the epidermis, dermis, and hypodermis, which integrate adnexal components such as pilosebaceous units, nails, and eccrine or apocrine sweat glands. While the protective epidermis directly meets the external environment, severe dermal and hypodermal exposures occur during deep-tissue wounding.[7] Characterized as the superficial integumentary stratum, the epidermis incorporates four to five layers of enucleated keratinocytes overlying two to three metabolically active cellular layers. The thickness of this barrier is highly region-specific, exhibiting minimal depth on the face and maximum thickness on the palmar and plantar surfaces. Mechanistically, it operates as a hydrophobic barrier that strictly modulates cutaneous hydration status.[8] The cellular composition of the epidermis is predominantly dominated by keratinocytes (around 90%), with the residual 10% distributed among specialized melanocytes, Merkel cells, and Langerhans cells.[9] Structurally, the dermis represents a fibroelastic connective tissue zone predominantly containing extracellular matrix, active fibroblasts, and endothelial populations. This vascularized stratum encapsulates critical adnexal and sensory units, including pilosebaceous complexes, sudoriferous glands, nerve fibers, and localized adipose tissue. This specific tissue layer constitutes 90% of the total cutaneous weight, functioning as the primary physiological bedrock of the skin organ system.[10] Fibroblastic lineages represent the principal cellular component of the dermal layer. They synthesize the extracellular matrix proteins collagen and elastin, which are critical for maintaining structural integrity and viscoelastic properties.[11] The hypodermal layer represents the innermost integumentary division, characterized as a loose connective tissue matrix rich in adipocytes, microvessels, and peripheral nerves. Functioning primarily in fluid retention and lipid accumulation, this tissue is heavily enriched with proteoglycans and glycosaminoglycans, thereby exhibiting distinct viscoelastic and mucoid behaviors.[12] The application of extreme thermal or mechanical forces induces severe trauma to the skin, frequently disrupting endogenous regenerative pathways and manifesting as clinical wounds. Pathological soft-tissue defects present through various clinical manifestations. These are primarily categorized into abrasions, surgical or clean incisions, hematomas, contorted lacerations, puncture sites, deep penetrations, and burn wounds.

The physiological cascade of wound repair systematically follows four distinct, overlapping steps to ensure full structural recovery of the injured integument.[13] Phase one is characterized by immediate hemorrhage and subsequent clot formation. The coagulation cascade initiates the conversion of soluble fibrinogen into an insoluble fibrin matrix. This 3D polymeric mesh encapsulates activated platelets, generating a physical plug that arrests blood

loss and prevents the open wound from interacting with the external environment. The second stage involves the inflammatory response, a localized transudate-mediated cascade. This mechanism assists in vascular control while driving the chemotactic migration of macrophages, fibroblasts, white blood cells, growth factors, and essential biomolecules to the wound bed to clear necrotic debris and eliminate infectious microorganisms. This concentrated cellular migration and fluid shift manifest as the classic signs of localized inflammation, discomfort, heat, and peripheral erythema adjacent to the injury site. Phase three involves proliferation, characterized by the active cellular reconstruction of the damaged dermis. This is mediated by fibroblastic populations that orchestrate the deposition of neo-collagen, elastin fibers, and auxiliary extracellular matrix networks. This step represents a pivotal milestone, as it orchestrates the onset of tissue granulation and demands robust angiogenesis to achieve functional tissue remodeling without excessive scarring. Mechanistically, myofibroblasts populate the provisional matrix, driving wound contraction by actively pulling the wound margins together. Sustaining a moisture-retentive microenvironment at this juncture facilitates rapid, physiological wound closure. The process culminates in stage four—the remodeling phase—wherein the initial type III collagen undergoes phenotypic conversion into type I collagen, allowing the provisional scar matrix to be replaced by a mature extracellular matrix morphology mimicking uninjured tissue. While standard tissue restoration spans a 21-day cycle, complex etiologies such as deep burns, ischemic ulcers, and non-healing chronic wounds require significantly longer intervention periods. The development of functional biomaterials, specifically hydrogels, is currently being driven by tissue engineering and regenerative medicine principles. These matrices are strategically engineered to prevent microbial colonization, sustain a moisture-retentive microenvironment, and optimize cutaneous healing kinetics.

Characteristics of an ideal dressing

High moisture vapour permeability

Non adherent

High capacity for absorption

Provide barrier to external contaminants

Prevents capillary loops penetrating into dressing material

Capable of being sterilized

Good adhesion to surrounding skin
Hypoallergenic
Comfortable to wear
Cost effective

2. HYDROGELS

These biomaterials exist in multiple modalities, including polymeric structures, glycerin/water-based gels, impregnated mesh, or solid sheets. Owing to their inherently high water content, their fluid-handling capacity is restricted; consequently, they are poorly suited for managing wounds characterized by heavy exudate production. Mechanistically, these dressings facilitate non-traumatic autolytic debridement and desloughing via the targeted rehydration of necrotic matrices. This process ensures the isolation and removal of non-viable tissue while fully preserving healthy cellular areas and capturing loose slough and localized exudates. Mechanistically, these matrices provide targeted rehydration to the wound bed while significantly mitigating patient pain via a localized cooling sensation. Additionally, their non-adhesive composition prevents secondary tissue trauma during changes, allows them to completely obliterate anatomical dead spaces, and facilitates uncomplicated application and removal.[14,15] These dressings are designed for minimally draining wounds and must be held in place with a secondary wrap. Hydrogels are emerging as vital biomaterials in medicine, celebrated for their safety profile, tissue compatibility, and high moisture retention. These matrices can also be engineered for biodegradability to suit specialized medical purposes. Over the last ten years, research into hydrogels has expanded rapidly, fueled by the diverse structural configurations made possible through versatile synthesis techniques. Consequently, material design and clinical application have advanced substantially.[16] Characterized by a 3D network of interconnected polymer strands, hydrogels possess a remarkable capacity to trap massive quantities of water within their internal matrices.[17] The utilization of diverse hydrophilic polymer building blocks provides hydrogels with highly adaptable chemical and physical profiles. Consequently, these systems can be engineered into various architectural shapes, such as macro-slabs, specialized coatings, membranes, and micro/nanoparticles.[18] These responsive materials—often termed "intelligent" networks—have found utility in personal care items, targeted drug delivery, catalysis, and biosensors. From a safety standpoint, they exhibit excellent tissue tolerance, triggering no significant inflammatory, toxic, or thrombotic side effects. A defining characteristic of these matrices is their stimuli-responsive behavior, enabling them to undergo reversible phase transitions or volume changes in response to fluctuations in pH, temperature, electromagnetic fields, ionic strength, or the presence of target biomolecules.[19]

2.1 Classification of Hydrogels

Hydrogels can be classified into different groups based on their:

i. Classification based on source

Hydrogels can be classified into two groups based on their natural or synthetic origins.

ii. Classification according to polymeric composition

The method of preparation leads to formations of some important classes of hydrogels. These can be exemplified by the following

a) Homopolymer hydrogels are polymer networks formed from a single type of monomer, which is the fundamental structural unit of any polymer network. Depending on the monomer's nature and the polymerization method used, homopolymers can have a cross-linked skeletal structure.

b) Copolymeric hydrogels are made up of two or more distinct monomer species with at least one hydrophilic component that are organised along the polymer network's chain in an alternating, random, or block pattern.

c) Interpenetrating polymeric hydrogel with several polymers. (IPN), a significant family of hydrogels, is composed of two separate, network-forming, cross-linked synthetic and/or natural polymer components. One component of semi-IPN hydrogel is a cross-linked polymer, while the other is a non-cross-linked polymer.

iii. Classification based on configuration

The classification of hydrogels depends on their physical structure and chemical composition can be classified as follows:

(a) Amorphous (non-crystalline).

(b) Semicrystalline: A complex mixture of amorphous and crystalline phases.

(c) Crystalline.

iv. Classification based on type of cross-linking

Hydrogels can be divided into two categories based on the chemical or physical nature of the cross-link junctions. Chemically cross-linked networks have permanent junctions, while physical networks have transient junctions that arise from either polymer chain entanglements or physical interactions such as ionic interactions, hydrogen bonds, or hydrophobic interactions.

v. Classification based on physical appearance

Hydrogels appearance as matrix, film, or microsphere depends on the technique of polymerization involved in the preparation process.

vi. Classification according to network electrical charge

Hydrogels may be categorized into four groups on the basis of presence or absence of electrical charge located on the crosslinked chains:

(a) Nonionic (neutral).

(b) Ionic (including anionic or cationic).

(c) Amphoteric electrolyte containing both acidic and basic groups.

(d) Zwitterionic (polybetaines) containing both anionic and cationic groups in each structural repeating unit.[20]

2.2 Synthesis of hydrogels

Hydrogels are created when homopolymers or copolymers are physically or chemically crosslinked, and they can be employed to provide three-dimensional structures particular mechanical and chemical properties. Covalent [21,22] or non-covalent.[23,25] interactions can create the crosslink. Non-covalent gels are referred to as physical gels, whereas covalently crosslinked hydro gels are also known as chemical gels. The copolymerisation may occur concurrently with or after the crosslink. Although chemical hydrogels have remarkable mechanical strength, they have negative side effects.[24] Hennink and van Nostrum have given comprehensive details regarding different physical and crosslinking techniques.[26]

- **Physical crosslinking**

Physical gels are three-dimensional networks formed by non-covalent interactions between polymer strands. When distinct polymer chains interact across a specific length rather than point-to-point (point crosslinks), junction zones are created. Hydrophobic interaction (Fig. 1a), in which hydrophobic and hydrophilic blocks are connected to form a polymer amphiphile, is one method of forming physical crosslinking. The hydrophobic blocks agglomerate as the temperature rises. The temperature at which the phase shift occurs depends on the polymer concentration, the hydrophobics' block length, and the polymer's chemical structure.[27] Additionally, polymers can connect through charge interaction (Fig. 1b) or hydrogen bond formation (Fig. 1c), which serves as a physical crosslink between the polymers. Charge interaction can take place between two oppositely charged polymers or

between a polymer and a tiny molecule.[27] Compared to covalent bonds, hydrogen and other non-covalent bonds are far weaker.

- **Chemical crosslinking**

Crosslinking is chemical in nature when the links between the polymers are covalent. Compared to non-covalent connections, covalent bonds are far stronger and offer superior mechanical stability. Chemical crosslinking techniques include the use of enzymes, high energy irradiation, complimentary group chemical reactions, and radical polymerisation.[25] Unlike physical crosslinking, chemical crosslinking requires crosslinking agents that can react with other chemicals.[24]

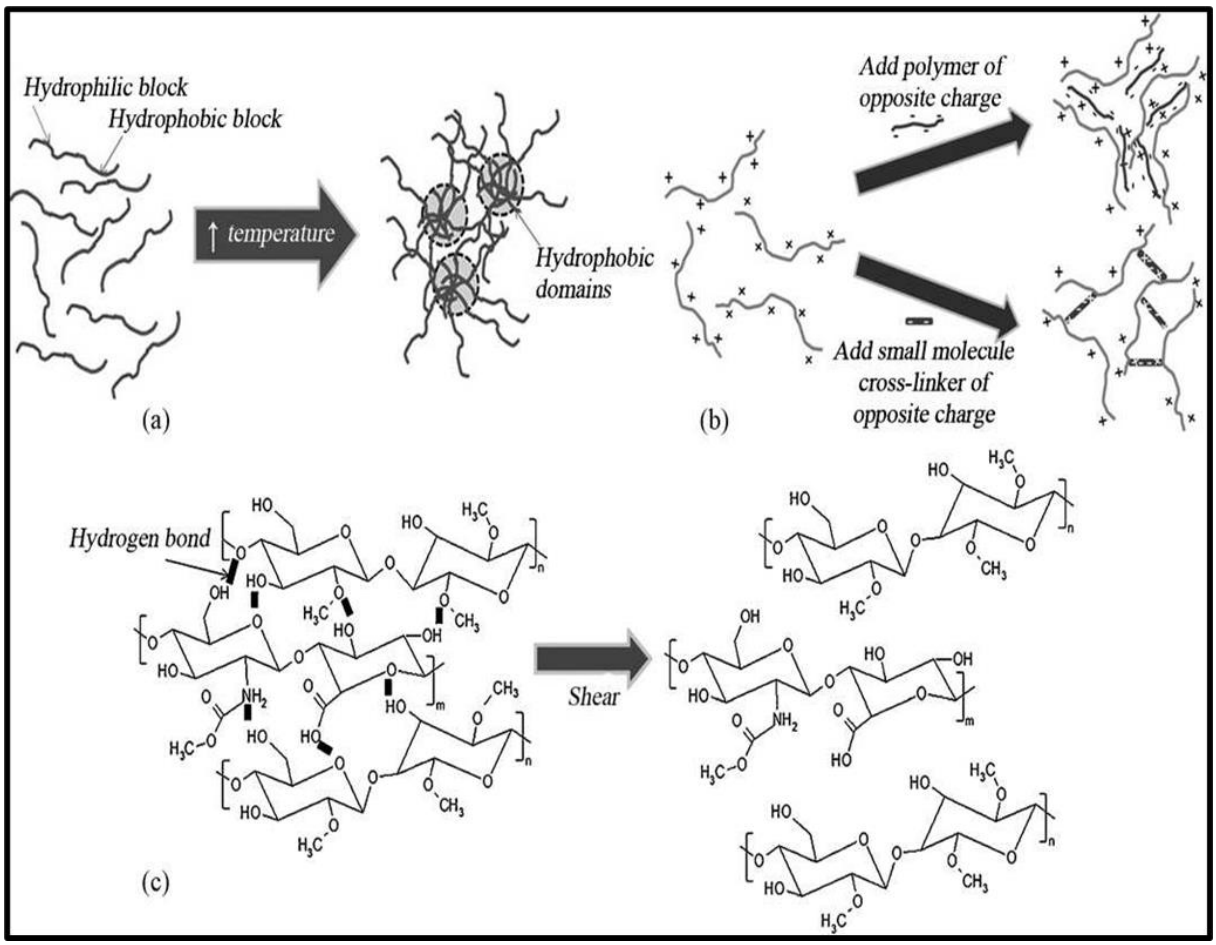

Fig. 1: (a) Hydrophobic interactions drive in situ physical gelation, (b) in situ physical gelation driven by charge interactions, (c) physical gelation driven by hydrogen bonding interactions, which can be disrupted by shear. Reprinted from with permission from Elsevier.

2.3 Operation principles

Hydrogels with numerous sensitivities, temperature-sensitive hydrogels, and pH-sensitive hydrogels are all members of the stimulus-sensitive hydrogels family. The physical behaviour and swelling mechanism of hydrogels that are sensitive to temperature and pH differ significantly.

The following paragraphs discuss the pH- and temperature-sensitive hydrogels independently.

Acidic or basic functional groups are added to the polymer backbone to create pH-sensitive polymers, which either take or release protons in response to suitable pH and ionic strength changes in aqueous conditions. Compared to polyelectrolyte gels, neutral polymer gels exhibit less swelling. The electrostatic repulsion between the polymer chains increases as a hydrogel becomes more ionised. The degree of swelling increases and the network becomes more hydrophilic. The number of pendant acidic or basic groups in these hydrogels determines how ionised they are. Basic hydrogels exhibit greater ionisation at low pH, while hydrogels with acidic groups become more ionised at higher pH. As a result, basic hydrogels behave differently from acidic hydrogels, which tend to swell more when the pH of the surrounding solution rises. In reaction to an external temperature stimulus, thermoresponsive gels undergo a phase shift. Both positive and negative temperature dependence are possible [28,29] Swelling rises with temperature when the temperature is positive, while it falls when the temperature is negative. Water-soluble polymers are those with a majority of hydrophilic groups, whereas water-insoluble polymers have a majority of hydrophobic groups. In terms of negative temperature sensitivity, the polymers' hydrophilic content makes them soluble in water at low temperatures; but, above a specific temperature, enhanced hydrophobic interactions cause them to collapse and show phase separation from the solution. The Lower Critical Solution Temperature is the name given to this temperature. N-alkyl acrylamides are a typical class of monomers utilized in the manufacture of temperature-sensitive hydrogels. N-isopropylacrylamide (NIPAAm) is a well-known monomer from this category. The side chains of this monomer interact favorably with water by forming hydrogen bonds. There is a negative temperature dependence on the hydrogen bonding process's efficiency. Enhanced dissolution in water results from hydrogen bonding between hydrophilic regions of the polymer chain and the water molecules at lower temperatures. Hydrogen bonding weakens and hydrophobic interactions between hydrophobic segments get stronger as the temperature

rises. The hydrogel will shrink as a result of the hydrogen bond-based crosslinks breaking up at higher temperatures.[30]

2.4 Applications of hydrogels

- **Applications of hydrogels in transdermal delivery**

Drug delivery to the skin has historically been used for topical application of dermatological medications to treat skin conditions or for skin disinfection. Transdermal delivery has been explored as a potential site for systemic medication delivery in recent years. Transdermal drug delivery has several potential advantages, such as the ability to avoid hepatic first-pass metabolism, supply medications for extended periods of time at a steady rate, and readily terminate drug delivery when needed by simply removing the devices. Additionally, compared to traditional ointments and patches, swelling hydrogels can feel nicer on the skin because to their high water content. Their employment as controlled release devices in the field of wound dressing is made possible by their high water content of approximately 96%, which permits the release of both hydrophilic and hydrophobic medications.[31]

- **Wound Dressing**

Due to its significance in the treatment of burns, prevention of post-surgical adhesions, and cosmetic surgery, wound healing is a field of ongoing research. Protecting wounds, encouraging healing, and supplying, holding, or eliminating moisture are among the functions of dressings. Some forms of wound dressings include biosynthetic dressings, composite dressings, gauze, hydrocolloid dressings, hydrogels, transparent films, etc. For more than 20 years, hydrogel dressings in various forms have been used to treat wounds. Numerous polymers serve as the foundation for hydrogel dressings. In order to provide the finished product some structural integrity, some polymers are crosslinked. This process typically results in a thin sheet that is applied to a very shallow wrapped surface.[32]

Because of the humectant qualities of hydrogel wound dressings, the wound is maintained moist to avoid scabbing or drying out, allowing it to heal from the inside out. When secretion is absorbed, the crosslinks in the polymer chains expand, creating space for foreign objects including bacteria, debris, and smell molecules that are permanently absorbed along the fluids. Because hydrogel does not stick to the surface of the wound, removing the hydrogel dressing is nearly painless. After extended use, hydrogel is readily removed without causing discomfort or increasing the risk of wound irritation. It also remains continuously moist. The hydrogel wound dressing is well-liked by patients for the reasons mentioned above.[33]

- **Contact lenses**

wycherley and Lim were the first to describe a hydrogel based on poly-2-hydroxyethylmethacrylate (PHEMA) as a synthetic biocompatible material that may be used for contact lens applications in their groundbreaking 1960 study. In 1962, PHEMA lenses were initially made available in western Europe, although they were not very successful. The National Patent Development Corporation (NPDC) purchased the technology's license in 1965. After that, it was sold to Bausch & Lomb, who improved Wycherley's spin-casting method and eventually received FDA certification for its PHEMA lenses in 1971.

Based on their flexibility, contact lenses are primarily categorised as "hard" or "soft." Hard lenses are more durable, but wearers typically don't like them and may need more time to get used to them. While soft lenses are based on hydrogel, hard contact lenses are mostly made of hydrophobic materials like poly (methyl methacrylate) (PMMA) and poly (hexa-fluor isopropyl methacrylate) (HFIM).[34]

- **Tissue engineering**

Every year, millions of people suffer from the loss or failure of an organ or tissue due to an illness or an accident. In the United States, more than 8 million procedures are performed to treat these individuals annually, and the total cost of these problems to the country's economy is estimated to be approximately $400 billion. Although tissue and organ transplants are well recognized treatments, the lack of donors severely restricts their use. "Application of the principles and methods of engineering and life sciences toward fundamental understanding of structure–function relationship in normal and pathological mammalian tissues and the development of biological substitutes for the repair or regeneration of tissue or organ function" is how the term "tissue engineering" was first defined in 1988. To put it another way, it entails the replacement or enhancement of particular tissues or organs through the use of synthetic techniques and created materials. Hydrogels have been used more recently in tissue engineering, where they can be used as space fillers, bioactive material delivery systems, or three-dimensional structures that arrange cells and provide stimuli to guarantee the growth of a desired tissue. Hydrogels' biocompatibility, which can be described as a material's capacity to come into contact with bodily organs without causing harm to the surrounding tissues or causing an unwanted reaction, is an essential characteristic. Poly (ethylene oxide), poly (vinyl alcohol), poly (acrylic acid), poly (propylene fumarateco-ethylene glycol), and polypeptides are synthetic materials that can produce hydrogels

appropriate for tissue engineering. Other naturally occurring polymers that could be utilised for this purpose include agarose, alginate, chitosan, collagen, fibrin, gelatin, and hyaluronic acid.[35]

- **Water Reservoirs in Agriculture**

Superabsorbent hydrogels are becoming more and more popular in agriculture. This is primarily because it is necessary to minimize water use and maximise water resources in horticulture and agriculture. It also plays a part in encouraging a new way of thinking about human habit and culture about water, which should be viewed as a resource to conserve rather than an excess to waste. It is well known that a hydrogel changes from a glassy to a rubber-like condition during the swelling process, which allows the material to retain water even under extreme stress. However, if there is a humidity gradient between the material's inside and exterior, the swollen hydrogels can gradually release water through a diffusion-driven mechanism.[36]

- **Controlled Release Drug Delivery System**

The perfect drug delivery system should be inert, biocompatible, mechanically robust, patient-friendly, able to achieve high drug loading, safe against unintentional release, easy to administer and remove, and simple to build and sterilise.[37] For novel protein, DNA, and other treatments, traditional medication delivery methods like tablets or injections are frequently inappropriate. Conventional multiple dosing regimens for long-acting therapy have a number of drawbacks, including systemic drug buildup that can cause toxicities or adverse effects, an uneven plasma drug level profile, and low patient compliance.[38]

The interest in controlled release medicine delivery systems has significantly increased during the past 20 years. This has been caused by a number of factors, including the high cost of creating new drug entities, the expiration of current international patents, the discovery of novel polymeric materials that can prolong drug release, and the enhancement of therapeutic efficacy and safety attained by these delivery systems. These days, veterinary products are also using controlled release technologies.[39]

2.5 Properties of Hydrogels

1. Swelling properties

Every hydrogel's polymer chains are chemically and physically cross-linked to one another. Because hydrogels have no molecular weight, they are sometimes referred to as super

macromolecules. Hydrogel can undergo quick, reversible changes in response to even slight environmental changes. The hydrogel's physical texture may change as a result of variations in environmental factors including pH, temperature, electric signal, enzyme presence, or other ionic species. These alterations could occur at the macroscopic level as hydrogels' water content, size, and precipitate formation. Hydrogels having basic or acidic functional groups react to changes in the pH of the surrounding environment. One kind of pH-sensitive hydrogel is polyacrylic acid, whose swelling ratio fluctuates due to the ionisation of carboxyl groups on the polymer chain.[61]

2. Mechanical properties

It is crucial to demonstrate the hydrogels' mechanical characteristics. Because of this characteristic, hydrogel exhibits a variety of biological uses, including cartilage replacement, ligament and tendon healing, wound dressing material, drug delivery matrix, and tissue engineering. These applications call for hydrogels with distinct properties. The process of injecting a pharmaceutical ingredient to achieve a therapeutic effect in or at a specific area within the human body is known as drug delivery. Drug delivery materials must have regulated characteristics, such as non-toxicity and a profile of absorption and release.

3. Biocompatible properties

To be a notable parameter in the biomedical area, hydrogels must be nontoxic and biocompatible. The cytotoxicity and in vivo toxicity tests must be met by the majority of polymers employed in this idea. The capacity of a substance to achieve a suitable host reaction in a certain application is known as biocompatibility. The two main components of biocompatibility are (a) bio-safety, which is the lack of cytotoxicity, mutagenesis, and/or carcinogenesis, and an acceptable host response that is both systemic and local (the surrounding tissue). and b) Bio functionality is the capacity of a material to do the particular activity for which it is suggested. In vitro biocompatibility testing can often be carried out in two methods and typically examine the material's cyto-toxicity characteristic in the presence of living host cells. The first approach involves placing the substance whose biocompatibility needs to be assessed in close proximity to the host environmental cells and then incubating it at 37°C for a predetermined amount of time. To allow for any leaching from the material, the second approach involves placing the material in an appropriate physiological solution and then incubating it at 37°C for a predetermined amount of time.

4. Water vapor transmission rate (WVTR)

It is the amount of water vapour that flows through a unit area of film material in a set amount of time under specific temperature and humidity conditions. The US standard ASTM E96-95 states that WVTR is measured in grams per square metre (g/m2) over a 24-hour period. It is inversely correlated with a wound dressing's ability to retain moisture; that is, a dressing with a lower WVTR will be able to keep the surface of the wound moist. A wound dressing material that has a WVTR of less than 35 g/m2/hr is typically considered moisture retentive and aids in quick healing.[61]

2.6 Preparation Methods of Hydrogel

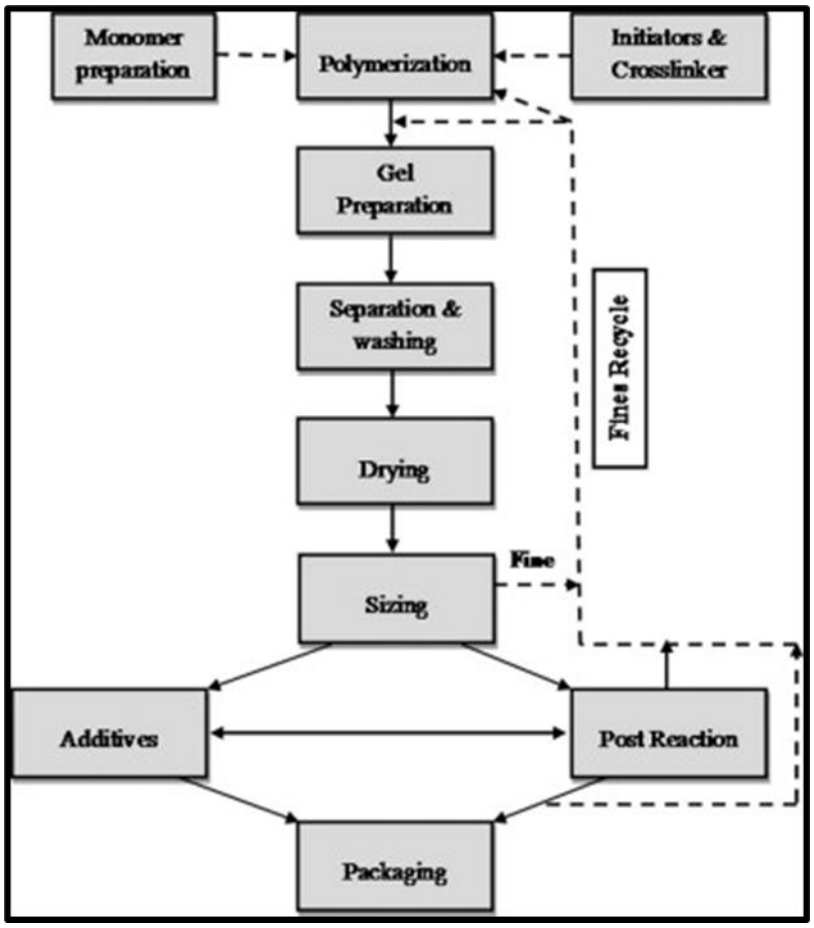

Fig No. 2: Hydrogel preparation block diagram (solution polymerization/cross-linking procedure).

- **Free radical polymerization**

The best technique for creating hydrogels based on different monomers such acrylates, amides, and vinyl lactams is conventional free radical polymerisation. Hydrogels based on natural polymers with suitable functional groups or those functionalised with radically

polymerisable groups can also be developed using it. For instance, hydrogels based on chitosan.[14]

- **Irradiation crosslinking**

Ionizing-radiation procedures are extremely valuable for the creation of hydrogels, especially when paired with a concurrent sterilization procedure. Unsaturated chemicals can be polymerised using high energy radiation, such as gamma and electron beam radiation. Water soluble polymers functionalized with vinyl groups can be transformed into hydrogels using high energy radiation. Ionizing radiations, such as electron beam and g–rays have high energy as much as necessary to ionize simple molecules either in air or water.[16] Numerous reactive sites are created beside the polymer strands when a polymer solution is exposed to radiation. Following that, a significant number of crosslinks are formed as a result of the conjunction of these radicals. However, because the generation of macroradicals requires less energy, irradiation of a polymer solution is supported. Furthermore, because the reaction mixture is less viscous in solution, radical efficiency is high.

- **Chemical crosslinking**

One of the main methods for creating hydrogels is chemical crosslinking. This approach involves adding a bi-functional crosslinking agent to a diluted solution of a hydrophilic polymer, which needs to have the right functionality to react with the crosslinking agent. This technique can be used to generate hydrogels from both synthetic and natural hydrophilic polymers. For instance, dialdehyde or formaldehyde were used as crosslinking agents to create hydrogels based on albumin and gelatin. Functionalized polyethylene glycol is crosslinked in hydrogels with a high water content to create a polypeptide that contains lysine.

Chain growth polymerization, addition and condensation polymerization, and gamma and electron beam polymerization procedures are used to create chemically cross-linked hydrogels. Polyfunctional crosslinking agents with monomer functional groups are added sequentially during addition and condensation polymerization.

- **Copolymerization/Crosslinking Reactions**

Copolymerization reactions are applied to produce polymer gels, many hydrogels are produced in this concept, for methyl acrylates).

- **Cross-linking with aldehydes**

Fixed conditions, such as low pH, the use of methanol as a quencher, and high temperature, are used to produce cross-linking. Glutaraldehyde can be used to cross-link hydrophilic polymers having –OH groups, such as polyvinyl alcohol. Alternatively, the same cross-linker that forms Schiff bases under mild circumstances can be used to crosslink polymers containing amine groups. It was specifically suggested for the production of cross-linked proteins, such as albumin and gelatin, as well as amine-enclosing polysaccharides.

- **Crosslinking Using Enzymes**

A novel technique for creating PEG-based hydrogels employing an enzyme has been revealed. When glutaminyl groups were added to a tetrahydroxy PEG, networks formed when transglutaminase accumulated in the PEG and poly (lysine cophenylalanine) solution. In order to create an amide connection involving the polymers, this enzyme catalyses the reaction between the γ-amine group of lysine and the γ-carboxamide group of PEG-Qa. The ratio of the PEG-Qa to the lysine copolymer may be able to alter the gel's characteristics. Gels with an equilibrium water content of 90% have been created under the right circumstances. When transglutaminase was added to an aqueous solution containing peptide-modified macromers, hydrogels were created. Sperinde et al. replaced the poly (lysine-co phenylalanine) with lysine end-functionalized PEG18. The macromer composition and structure, the reactant ratio, and the concentration of the enzyme all affect the gelation kinetics. Transglutaminases are enzymes that require Ca2+. Westhaus et al. envisioned a triggered hydrogel gelling system.

- **Physical Crosslinking of Hydrogels**

Ionic contact, crystallization, stereo complex formation, hydrophobized polysaccharides, protein interaction, and hydrogen bonding all contribute to the development of physically crosslinked hydrogels.

- **Crosslinking by ionic interactions**

Hydrogels can be gradually crosslinked in ionic interactions at ambient temperature and physiological pH. Ionic groups in the polymer are not required for this cross-linking process. Stronger hydrogel is produced by metallic ions. One notable example of a polymer that can be crosslinked by ionic interactions is alginate.

Alginate is a naturally occurring polysaccharide that is crosslinked by calcium ions and contains residues of mannuronic and glucuronic acid. At ambient temperature and physiological pH, crosslinking is visible. Alginate gels are therefore frequently used as a matrix for the release of proteins and the encapsulation of live cells. Interestingly, the gels can be destabilised by using a chelating agent to extract the Ca-ions from the gel. The release of proteins from alginate microparticles, which is accomplished by spraying a sodium alginate solution into an aqueous calcium chloride solution, can be changed by coating the particles with cationic polymers, such as polylysine and chitosan.

2.7 Advantages of Hydrogel

Environmentally sensitive hydrogels exhibit the capacity to sense changes in temperature, pH, or metabolite concentration and release their load in response. Hydrogel has more flexibility and strength. The benefit of minimal toxicity is made possible by encasing microbial cells in polyurethane hydrogel beads. Natural hydrogel materials are being examined for tissue engineering, these materials incorporate agarose, methylcellulose, hyaluronan, and other naturally derived polymers. Hydrogel based microvalves shows a number of advantages over conventional microvalves, incorporating moderately simple fabrication, no outer power requirement, no integrated electronics, large displacement and large force generation.

2.8 DISADVANTAGES

The primary drawbacks are the excessive price and the feeling of the maggots' movement. It includes the surgical risk related to the insertion and retrieval of the device as well as thrombosis at anastomosis sites. Because hydrogels are nonadherent, a secondary dressing may be necessary to protect them. Red eye responses, hypoxia, dehydration, and lens deposition are drawbacks of hydrogel in contact lenses.[61]

3. ANTIMICROBIAL AGENT

Micromonospora purpurea or M. echinospora ferments to create tobramycin, an aminoglycoside antibiotic complex. C1, C1a, and C2 are the three main components that make up this mixture. The sulphate salt is tobramycin. Each component has five basic nitrogen atoms and needs five sulfuric acid equivalents for every mole of gentamicin base.[31] Tobramycin is an aminoglycoside antibiotic that is frequently applied topically to treat bone and soft tissue infections as well as severe Gram-positive and Gram-negative microbiological infections, particularly in burns and wounds. Impetigo, infected bed sores, burns, nasal

staphylococcal carrier status, pyodermata, external eye infections, and adenexa are all frequently treated with topical tobramycin. Despite its advantages, tobramycin's daily dosage is limited by bacterial barriers and side effects include nephrotoxicity, ototoxicity, and neurotoxicity after extended use.[40] Topical hydrogels could be used as an alternate low-dose regimen to ensure that the advantages of tobramycin—particularly its quick bactericidal action, especially in bloodstream infections—are properly utilised while also minimising the toxicity linked to long-term tobramycin use. Large amounts of tobramycin solution may be retained by these hydrogels, which can be applied directly to the skin without the need for complex apparatus.[41]

3.1. Hydrogels with Intrinsic Antimicrobial Activity

3.1 Properties of Antimicrobial Hydrogels

Each of the hydrogels under discussion plays a complex role in the wound healing process through a variety of interactions, such as promoting angiogenesis and cell proliferation, activating neutrophils and macrophages to start the healing process, inhibiting metalloproteinases, controlling the oxidation-reduction environment, or improving microbiological purity.

3.1.1. Polysaccharide Hydrogels

One well-known and well researched example of the class of polysaccharide hydrogels is chitosan, which is commonly employed for its appropriate antibacterial activity. Chitosan is a naturally occurring polymer that is produced by enzymatic or chemical deacetylation of chitin, the building block of insects and crustaceans. Both chitin and chitosan have found numerous prospective biological uses due to their exceptional biochemical qualities, including biocompatibility, biodegradability, non-toxicity, and processability.[42] Chitosan polymers are positively charged areas on the microbial membrane because they contain amino groups.[43]

3.1.2. Antimicrobial Peptide Hydrogels

A class of tiny natural (made by multicellular animals) or artificial polypeptide molecules is known as antimicrobial peptides. They function as different creatures' innate immune systems.[44,45] They are therefore a great basis for producing natural hydrogels with antimicrobial qualities. At least several hundred of these proteins have been found to date.[47] being great therapeutic candidates for clinical use because of their many benefits, including as simplicity of synthesis and modification, biocompatibility, and biodegradability.

Antimicrobial peptides have a different antibacterial mechanism than antibiotics. As a result, microorganisms have a considerably harder time developing drug resistance.[48] Certain antimicrobial peptides have the ability to self-assemble into supramolecular hydrogels, which typically increase their antibacterial activity 45. For instance, Sallick et al. demonstrated the strong intrinsic antibacterial activity of a peptide hydrogel based on β-hairpins.[46] Gels were shown to be efficient against a variety of pathogens during the studies, including Gram-positive (Staphylococcus epidermidis, Staphylococcus aureus, and Streptococcus pyogenes) and Gram-negative (Klebsiella pneumoniae and Escherichia coli) bacteria. According to the theorized mechanism of antibacterial activity, cellular interaction with the gel surface causes membrane rupture, which results in cell death.[46]

3.2. Hydrogels Loaded with Antimicrobial Agents

Hydrogels can significantly boost their antibacterial efficiency when loaded with antimicrobial drugs. Antibiotics, biological extracts, nanoparticles, and antimicrobial peptides are the four primary categories of antimicrobial agents/factors that can be placed into a hydrogel matrix; each are covered separately in this chapter.

3.2.1. Hydrogels Loaded with Antibiotics

The majority of natural hydrogels are biocompatible, which makes them an easy place to start when creating a variety of antimicrobial systems based on different active chemicals, the most popular of which are, of course, antibiotics.[49] Antibiotics can combat bacterial illnesses by either slowing or stopping the growth of germs (bacteriostatic effect) or killing them (bactericidal impact),[50] 51functioning selectively at different doses and influencing different bacteria' cellular structures and metabolic processes[50,53] Many natural hydrogels' regulated hydrophilic/hydrophobic properties make them ideal for incorporating a variety of small compounds, including antibiotics. In particular, the effectiveness of local antibiotic therapy in treating and preventing bacterial infections is becoming more widely acknowledged. Medical dressings for topical application (mostly wound treatment) have increased in popularity and importance.[54] because antibiotic-loaded hydrogels can provide multiple advantages simultaneously. Wound healing is hampered by bacterial infections.

4. TOBRAMYCIN

Drug Profile

Table No. 1: Drug Profile.

Sr.No.	Parameter	Description
1.	Drug Name	Tobramycin
2	Category	Aminoglycoside antibiotic
3.	Chemical Nature	Basic, water-soluble compound
4.	Molecular Formula	C18H37N5O9
5.	Molecular Weight	~ 467.5 g/mol
6.	Biological half life	2 to 3 hours
7.	Solubility	Freely soluble water

A common treatment for severe infections brought on by Gram-negative bacteria is tobramycin, a broad-spectrum aminoglycoside antibiotic. It is frequently used in topical, ophthalmic, and parenteral dose forms and is very effective against Pseudomonas aeruginosa. When administered in appropriate dose forms, tobramycin is regarded as the medication of choice for localised infections because of its strong antibacterial activity and quick bactericidal action.

4.1 Against Different Microorganisms

- *Pseudomonas*
- *E. coli*
- *Staphylococcus aureus.*

4.2 Mechanism of Action

Tobramycin works by attaching to the 30S ribosomal subunit after passing through the bacterial cell membrane. This binding disrupts the protein synthesis starting complex, misinterprets the genetic code, and produces toxic or non-functional peptides. Tobramycin has a bactericidal effect because it disrupts the integrity of the bacterial cell membrane and causes cell death.

4.3 Spectrum of Activity

When it comes to aerobic Gram-negative bacteria, tobramycin is very effective. It works very well against Enterobacter species, Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, and Proteus species. Additionally, it exhibits weak efficacy against several Gram-positive bacteria, including Staphylococcus aureus.

4.4 Therapeutic Uses

Diseases of the skin and soft tissues, burn wounds, eyes, respiratory tract (in cystic fibrosis), and other significant diseases brought on by susceptible organisms are all treated with tobramycin. It is mostly utilised in topical formulations to treat bacterial infections that are localised and have little systemic absorption. Topical Tobramycin is indicated in the topical treatment of folliculitis, furunculosis, paronychia, and other minor bacterial skin infections (including infected insect bites, infected minor burns, infected contact dermatitis, infectious eczematoid dermatitis, infected seborrheic dermatitis, infected excoriation, infected lacerations, infected skin abscesses and cysts, infected skin ulcers, infected stasis ulcers, infected stings, bacterial superinfections of minor fungal and viral infections, sycosis barbae, and minor surgical wounds) caused by staphylococci, streptococci, Proteus vulgaris, Escherichia coli, Pseudomonas aeruginosa, and Enterobacter aerogenes (Aerobacter aerogenes).

4.5 Pharmacokinetics

Tobramycin is given parenterally or topically since it is not well absorbed by the digestive system. Systemic absorption is low when given topically, which lowers the possibility of systemic harm. It does not undergo significant metabolism and is primarily eliminated unchanged via renal excretion when absorbed systemically.[55]

4.6 Adverse Effects

Tobramycin used systemically may result in neuromuscular inhibition, nephrotoxicity, and ototoxicity. However, because there is less systemic exposure when the medication is applied topically, these side effects are much diminished.

4.7 Toxicity

Five to twenty-five percent of patients may experience mild and reversible nephrotoxicity. In proximal renal tubular cells, tobramycin builds up and damages the cells. Despite ongoing drug exposure, tubular cell regeneration takes place. Usually, toxicity develops a few days after starting treatment. may result in permanent ototoxicity. There seems to be a connection between lifetime cumulative exposure and ototoxicity. Drug buildup in the inner ear's endolymph and perilymph damages the cochlea's hair cells or the vestibular complex's summit of ampullar cristae irreversibly. Low frequency hearing loss follows the loss of high frequency hearing. Retrograde degeneration of the eighth cranial (vestibulocochlear) nerve may result from further poisoning. Vertigo, nausea, vomiting, dizziness, and loss of balance

can all be symptoms of vestibular poisoning. Rat intravenous LD50: 96 mg/kg; mouse intravenous LD50: 52 mg/kg.

4.8 Metabolism

These drugs are not metabolized, and more than 90% of the dose is recovered in urine as unchanged drug within 24 hr.

5. EXCIPIENTS PROFILE

Excipients play a crucial role in the formulation of hydrogel dosage forms by influencing drug release, stability, viscosity, spreadability, and patient acceptability. In the present study, suitable excipients were selected to ensure the formation of a stable, effective, and patient-friendly tobramycin hydrogel with good antimicrobial performance.[56]

List of Excipients Used in the Formulation

Table No. 2: List of Excipients Used in the Formulation.

S. No.	Excipient Name	Category	Chemical Nature	Typical Concentration	Function in Formulation
1	Carbopol 934 / Carbopol 940	Gelling agent	Cross-linked polyacrylic acid polymer	0.5–2.0 % w/w	Provides gel structure, viscosity and consistency
2	Hydroxypropyl Methylcellulose (HPMC)	Polymer / viscosity enhancer	Semi-synthetic cellulose derivative	1–5 % w/w	Improves gel strength, spreadability and controlled release
3	Propylene Glycol	Humectant / co-solvent	Polyhydric alcohol	5–15 % w/w	Enhances solubility, moisture retention and skin penetration
4	Methyl Paraben	Preservative	Para-hydroxybenzoate ester	0.1–0.2 % w/w	Prevents bacterial and fungal growth
5	Propyl Paraben	Preservative	Para-hydroxybenzoate ester	0.02–0.05 % w/w	Enhances preservative efficacy against molds and yeasts
6	Triethanolamine	Neutralizing	Organic amine	q.s.	Adjusts pH

		agent			and facilitates gel formation
7	Distilled Water	Vehicle	Purified aqueous medium	q.s. to 100 %	Solvent and dispersion medium

5.1 Carbopol (934 / 940)

Carbopol is a cross-linked polyacrylic acid polymer with a high molecular weight that is widely employed as a gelling agent in topical and transdermal medication administration systems. Even at low concentrations, carbopol swells in water after neutralisation to create a transparent, clear gel with exceptional viscosity. Good bioadhesive qualities provided by carbopol enable the formulation to stay at the application site for an extended amount of time. It is perfect for hydrogel formulations since it is chemically stable, non-toxic, non-irritating, and compatible with a variety of active medicinal ingredients.

5.2 Hydroxypropyl Methylcellulose (HPMC)

Pharmaceutical formulations frequently employ HPMC, a semi-synthetic, nonionic cellulose ether, as a thickening and stabilising ingredient. HPMC improves the gel matrix's homogeneity and mechanical strength in hydrogels. By creating a viscous diffusion barrier surrounding the drug particles, it helps regulate drug release. Because HPMC is non-toxic, non-irritating, and biocompatible, it increases formulation acceptance and patient compliance.

5.3 Propylene Glycol

A common humectant and co-solvent in topical medication delivery systems is propylene glycol, a colourless, odourless, hygroscopic liquid. It keeps the formulation hydrated by minimising moisture loss and increases the solubility of hydrophilic and slightly lipophilic medications. By changing the characteristics of the epidermal barrier, propylene glycol also improves medication penetration and therapeutic efficacy.[57,58]

5.4 Methyl Paraben

A common antimicrobial preservative that works well against a variety of bacteria and fungi is methyl paraben. It shows good compatibility with the majority of pharmaceutical excipients and is stable over a broad pH range. Methyl paraben ensures product safety and prolongs shelf life in hydrogel compositions by preventing microbial contamination during storage and repeated use.

5.5 Propyl Paraben

For a synergistic preservation effect, propyl and methyl paraben are frequently combined. It enhances the antibacterial properties of methyl paraben and works especially well against moulds and yeasts. The hydrogel formulation's complete antibacterial protection is ensured by the combined use of parabens.

5.6 Triethanolamine

Triethanolamine is an organic amine used as a neutralizing agent in carbopol based gels. It adjusts the pH of the formulation to the physiological skin pH range, ensuring patient comfort and minimizing irritation. Neutralization with triethanolamine promotes carbopol swelling, resulting in optimal gel consistency and stability.

5.7 Distilled Water

The hydrogel formulation's main vehicle and dispersion medium is distilled water. It makes it easier for the medication to be evenly distributed throughout the gel matrix by dissolving hydrophilic excipients. Using purified distilled water improves the formulation's overall stability and safety while lowering the possibility of contamination.[59,60]

6. Hydrogel Matrices for Tobramycin

1. Natural Hydrogel Matrices

Natural polymers offer excellent biocompatibility, low toxicity, and innate biodegradability. They are often chosen for wound care, tissue engineering, and topical applications.

- **Alginate (Anionic Matrix - Best for Sustained Release)**

MECHANISM: Alginate is a negatively charged polysaccharide.

Tobramycin Interaction: The positive charges on Tobramycin form strong electrostatic (ionic) interactions with the negative carboxylic groups of alginates.

ADVANTAGE: This strong ionic bonding slows down the diffusion of Tobramycin, preventing a sudden burst release and allowing the antibiotic to release slowly over several days to fight chronic infections like Pseudomonas aeruginosa biofilms.[62]

- **Chitosan (Cationic Matrix - Synergistic Antimicrobial Effect)**

MECHANISM: Chitin is the source of chitosan, a positively charged polymer.

Tobramycin Interaction: Because both Chitosan and Tobramycin are positively charged, they repel each other.

ADVANTAGE: This repulsion causes Tobramycin to release very quickly (burst release), which is useful for rapidly killing bacteria at the beginning of treatment. Furthermore, Chitosan has its own natural antimicrobial properties (disrupting bacterial cell walls), which creates a powerful synergistic effect when combined with Tobramycin.[63]

- **Hyaluronic Acid & Gelatin (Tissue Repair Integration)**

MECHANISM: Naturally occurring components of the extracellular matrix.

ADVANTAGE: They are ideal for wound healing dressings. When loaded with Tobramycin, they protect the tissue from bacterial infection while simultaneously stimulating cellular migration and proliferation to heal the skin.

2. Synthetic Hydrogel Matrices

Synthetic polymers offer highly reproducible, predictable architectures. They can be engineered to have exact mechanical strength and precise pore sizes.

- **Polyethylene Glycol (PEG)**

MECHANISM: A neutral, highly hydrophilic synthetic polymer.

Tobramycin Interaction: PEG does not have electrical charges, meaning Tobramycin is held purely by physical entrapment within the water-filled mesh.

ADVANTAGE: PEG matrices can be structurally modified to change their cross-linking density. By tightening or loosening the PEG mesh, researchers can mechanically control exactly how fast Tobramycin diffuses out.

- **Polyvinyl Alcohol (PVA)**

MECHANISM: A synthetic polymer that dissolves in water and is frequently processed using freeze-thaw cycles (cryogels).

ADVANTAGE: PVA hydrogels are remarkably elastic and strong mechanically. In order to treat bacterial keratitis or conjunctivitis, they are frequently utilised to create medicated contact lenses or ocular inserts that gradually release tobramycin into the tear film.

- **Poly(N-isopropylacrylamide) (PNIPAM)**

MECHANISM: A traditional "smart" polymer that responds to heat.

ADVANTAGE: At room temperature, PNIPAM is a liquid; however, at human body temperature (37oC), it solidifies into a hydrogel. Tobramycin-containing liquid can be injected into an infected site. After entering the body, it solidifies into a localised gel "depot" that releases the antibiotic gradually over time.[63]

7. CONCLUSION

Hydrogel based drug delivery system have emerged as a promising approach for improving the therapeutic effectiveness of antimicrobial agent such a Tobramycin. Due to high water content, biocompatibility, biodegradability, and controlled drug release properties, hydrogels provide an efficient platform for localized and sustained delivery of antibiotics. Tobramycin loaded hydrogels have shown significant antimicrobial activity against various pathogenic microorganisms, especially *pseudomonas aeruginosa* and other gram-negative bacteria commonly associated with wound infections, ocular infections and cystic fibrosis related infection. Furthermore, recent advancements in smart and stimuli-responsive hydrogel have opened new possibilities for targeted and responsive antimicrobial therapy.

The crosslinked polymer networks containing hydrogels that soak up substantial amounts of aqueous solutions. There are large number of novel hydrogel systems have been observed.

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CONFLICT OF INTEREST

I am author and corresponding author and this work never published before and this is a new work.

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