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The Effectiveness of Probiotic and Prebiotic for oral ulcer healing in hydrogel form

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Abstract

The purpose of this study represents whether incorporating probiotics and prebiotics into a hydrogel can accelerate the healing process of mouth ulcers. By improving the targeted release of advantageous microorganisms, the hydrogel delivery system explores their potential to decrease inflammation and speed up the healing process. The review seeks to offer useful knowledge on the creation of novel and potent polysaccharide formulations for the treatment of oral ulcers.

Key words: oral ulcer, hydrogel, polysaccharides, Chitosan, Carrageenan, haluronic acid, alginate, xanthan.

Introduction

Oral ulcer

Most mouth ulcers cause pain and have a negative impact on eating and drinking. Oral ulcers, also referred to as Aphthous stomatitis. This is a common condition that can arise from a variety of factors. They indicate a full-thickness rupture in the epithelium lining the soft tissues of the mouth and afflict a significant number of the population.[1]

One of the most prevalent oral conditions, oral ulcers have a high complexity, diversity, and prevalence rate. Oral ulcers have a variety of etiological reasons, including traumatic, allergic, and viral events. They can also be linked to systemic, autoimmune, or mucocutaneous illnesses.[2]

Oral ulcers are characterized by a crater-like appearance, connective tissue loss, and chroic abnormalities or disintegration of the mouth epithelial integrity. Corticosteroids and antibiotics are typically the cornerstones of

clinical treatment for mouth ulcer. While corticosteroids can have harmful side effects and toxicity, they are also capable of causing hyperglycemias, blood pressure disturbances, gastrointestinal bleeding, and disruption of electrolytes. Bacteria with Antibiotic – resistant might restrict the usage of drugs in treating oral ulcers. Thus it's imperative to create efficient treatment.[2]

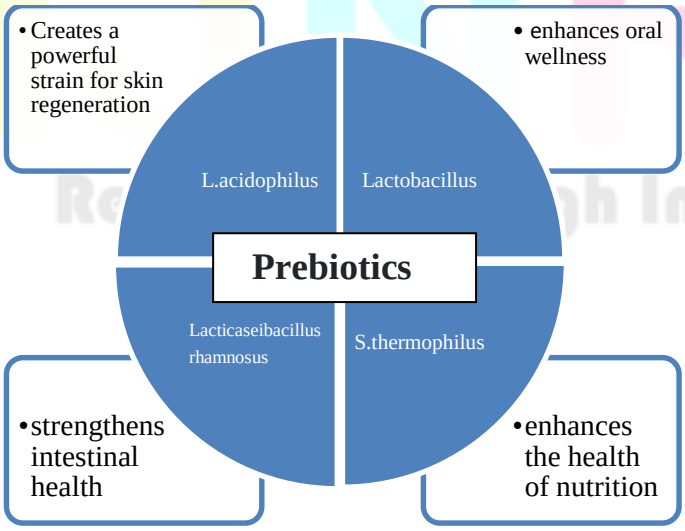
Probiotics

Probiotics can described as "Living microorganism may confer beneficial health effects for individuals being treated when administered in adequate amounts ." Research has demonstrated that probiotics can enhance immune system performance , alleviate diarrhea ad irritable bowel syndrome , avert colon cancer, decrease cholesterol level, and alleviate symptoms of anxious and depressed.[3]

Probiotics work through a variety of ways to modify the skin microflora, which improves skin integrity, reduces inflammation, and inhibits the formation of biofilms. In addition, they have been demonstrated to promote angiogenesis and cell proliferation, which when combined with the previously mentioned properties and promote wound healing. Probiotics have shown to increase wound-healing efficacy in a number of human and animal models. Probiotics that have been studied in relation to diabetic ulcers, infected and non-infected wounds, and thermal injury models include Lactobacillus plantarum, Lactoferrone, and Saccharomyces cerevisiae.[4]

Prebiotics

The term "Prebiotic has been described as a inactive food component that effectively promotes the development and Metabolic processes of a particular kind of microorganism there by enhancing host well-being and providing a positive impact on the host." Prebiotics can precisely modify gut microbita and inhibit pathogens within normal individuals through the generatinon of immunomodulatory molecules that have a pathogen-antagonistic properties , such as lactic acid generated by the Lactobacillus and Bifidobacterium genera.[5]

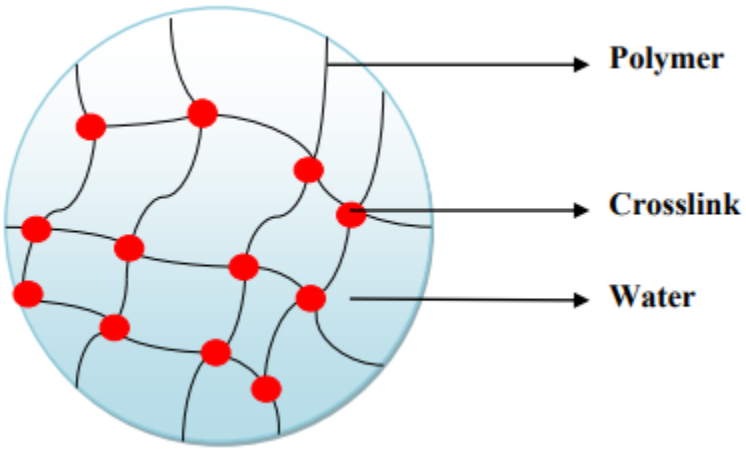


Effectiveness of hydrogel drug delivery

Hydrogels can be prepared as films by utilizing biopolymers. Hydrogels are preferred because of their regulated medication release, biocompatibility, and capacity to prevent drug deterioration. Furthermore, certain hydrogels mucoadhesive qualities help to immobilize them at the administration site. Ionotropic gelation, a method that includes cross- linking via the interaction of ions with opposite charge, appers to be a viable method for isolating probiotic bacteria within a hydrogel matrix.[6]

Hydrogel

Hydrogels have a three dimensional structures, comprising an insoluble interconnected structure in water soluble copolymers which are capable to absorb or retain a substantial portion containing water in their swollen forms.[9] In the polymer networks, water or biological fluid serves as a dispersion medium. The remarkable ability of the polymer chain to retain water is mainly because of nature of hydrophilic bond , which include the carboxyl, hydroxyl as well as amino groups.[10] Additional variables linked to water retention encompass the crosslinking density, physical crosslinking structure, solution composition, and co-polymer production method. Hydrogels can be designed with their basic structure and water-retaining ability on-demand by varying the hydrogel polymer's composition and crosslinking technique[11]



Mechanism of hydrogels

Mechanism of hydrogel in probiotics release

There are two ways that hydrogels for oral mucosal ulcers function. They first act as a barrier to protect the ulcer from further irritability and to aid in its healing. Second, hydrogels can support the preservation of moisture, which is advantageous for the healing of wounds.[7]

The process y which probiotics are released from a hydrogel composition depends on multiple variables. The hydrogel matrix serves as a barrier of defense, enabling the probiotics to discharge gradually and under control[8]. The probiotics can diffuse out of the hydrogel when it swells and forms pores or channels as it hydrates. The size and charge of the probiotic particles, as well as the hydrogel's composition and crosslinking, all have an impact on this diffusion process. The bacteria's natural qualities along with the hydrogel matrix enable targeted distribution and controlled release, which increases the probiotics potential therapeutic advantages[8].

Polysaccharide based Hydrogels

a. Chitosan

Chitosan is a possible option for medication administration. It is thoroughly investigated for the delivery of drugs. It has strong bacteriostatic, fungistatic, anticarcinogenic, and hemostatic qualities in addition to being compatible and biodegradable.[12] Chitosan-based Hydrogels have been ideal for the distribution of medical compounds because they have a soft texture and less friction in water as well as biological fluids. Chitosan hydrogels allow for the intelligent distribution of medications in response to various stimuli.[13] Chitosan hydrogels that are sensitive to pH are utilized to deliver drugs to certain locations in the stomach, colon, small intestine, and mouth. Medications that target infection and inflammation locally are sometimes recommended in addition to antibiotics and antiseptics for the treatment.[14]

b. Carrageenan

Carrageenan is a sea weeds contain sulfated linear polysaccharides, belongs to Rhodophycea family of red sea weeds yields Carrageenan. A sulfated and anionic polysaccharide that is flexible and generates a curly structure is called carrageenan.[15] It possesses thickening, stabilising, and gelling properties.[16] Carrageenan is mostly utilized in wound care, tissue engineering, and medication delivery. Their robustness, compatibility, and consistent viscoelasticity rendered them appropriate for use in pharmaceutical and prolonged release formulations. Carrageenan exhibits strong antioxidant properties. Carrageenan and natural- synthetic polymer blends have gamered significant interest for use in drug distribution, tissue development, and various therapeutic uses. [17]

Carrageenan is categorized into three classes according to the amount of sulphate it contains: lambda (λ), iota (ι), and kappa (κ).For milder and more intense gels, for example, ι and κ are utilized. κ-carrageenan comprises substitute 4-linked Three-linked beta-d-galactose and 6-anhydro-N-galactopyranose 4-sulfate has one negative charge associated with every disaccharide molecule that is repeated. Each disaccharide in ι-carrageenan has two sulphate groups. Similar qualities, such as gelling and thermo-reversible network formation, are shared by ι and κ-carrageenan. This nature and concentration of cations have an impact on gelation. Each disaccharide in λ-carrageenan contains three sulphate groups. Better solubilities and strength in gels were conferred by lower ester sulphate group levels. Potential uses for carrageenan exist in the food, non-food, and medicinal industries. Carrageenan is a great physical and functional ingredient that can be employed as a gelling, thickening, stabilising, and emulsifying agent. The polymer framework's relaxation and contraction, as well as electrostatic interactions, govern the release of drugs from carrageenan hydrogel. Using cross-linkers, the physical characteristics of carrageenan can be modified to promote drug release. Similarly, controlled release of medications was achieved with genipin fabricated PVA hydrogel incorporating κ-carrageenan.[17]

c. Hyaluronic acid

Hyaluronic acid comprises a linear polymer made upof glucoronic acid as well as N-acetylglucosamine disaccharide. The principle functions on HA are tissue regeneration, which includes stimulating angiogenesis, migration, and cell proliferation, as well as initiating and modulating inflammatory responses.[18] Additionally, it encourages re-epithelization by encouraging basal keratinocyte growth. Recently, hyaluronic acid hydrogels have attracted attention as novel biocompatible and biodegradable polymers with potential uses in tissue engineering and medication administration. Hydrogels cannot be produced by hyaluronic acid alone; instead, chemical processes are required to produce chemically cross-linked networks.[19] In treating gingivitis and periodontitis, HA demonstrates advantageous anti-inflammatory and antibacterial activities. PVP, a significant component of this preparation, is recognised for its exceptional qualities, including high media compatibility, low toxicity, good chemical and biological inertness, and crosslink able versatility, which gives the formulation strength. A protective layer called topical PVP-SH gel or 0.2% of HAsurrounds the mouth cavity, preventing exposed or sensitized nerve endings from being overstimulated.[20] The roles that each element in PVP-SH plays are mentioned below.

- Polyvinylpyrrolidone-The hydrophilic polymer improves tissue hydration because of its mucoadherent and film-forming qualities.
- Hyaluronic acid - where as sodium hyaluronate(SH) enhances the hydration of tissues, protects the mucus membrane in the mouth, and aids in recovery.
- Glycyrrhetinic acid - Results from the degradation of vital ingredient in licorice glycyrrhizin, also possesses anti-inflammatory qualities which promotes an ulcer wound healing. It serves as flavouring component as well.

0.2% HA or PVP-SH gel has the advantage with tropical steroids this can be ustilized safely on every patient types, which involves pregnant women and infants, who may be unwiling to take steroids. It is beneficial for every type of mouth ulceration.[21]

d. Alginate

Alginate represents an anion-like linear polysaccharide containing α-L-guluronic acid as well as β(1,4) linked β-D-mannuronic acid residues. Alginate can be produced industrially by removing it through the cell membranes of brown algae. Additionally, biosynthesis has been suggested as a viable technique for generating this polysaccharide, as it produces alginate through greater level chemical arrangements compared to algae derived alginate. Alginate is a polymeric material that is toxic- free, biologically compatible, easily biodegradable. It was been utilized in numerous therapeutic uses includes regeneration of wound , pharmaceutical distribution systems, and tissue regeneration. Alginate–composed hydrogels has many different applications.[22]

Alginate Hydrogels, which are ineffective in acidic environments, can be used as probiotic delivery systems to protect bacteria from stomach acid. The visible appearance of alginate gels is due to the capability of α-L-glucronate residues to interact with multivalent cations like Ca_2^+.The pH of the solution that surrounds it has a significant influence on the behavior of ionically linked polymeric hydrogels. Probiotic delivery techniques may employ chitosan-coated or uncoated alginate hydrogels. Alginate and other non-polysaccharide biopolymers seems to be ready to combined in order to generate hydrogels useful for these kinds of applications. The protein molecules, which consists of globular proteins mainly made up of β-lactoglobulin as well as α-lactalbumin, have the potential to be utilized as a coating agent for calcium alginate beads.[23]

It has been demonstrated that alginate-based hydrogels are appropriate materials for probiotic bacteria delivery systems that are taken orally. However, in order to adequately protect encapsulated probiotic organisms from adverse environments, alginate hydrogels should be coated, for example with proteins or chitosan. Alginate beads with many layers have the ability to effectively shield encapsulated microorganisms from acidic environments.[24]

e. Xanthan

Xanthan is a branched polysaccharide chains having a D-glucuronic acid positioned in middle of two D-mannose units connected to each glucose residue, and whose backbone is containing of β-(1,4) linked D-glucose units. For instance, bacteria can digest agro-industrial waste materials like corn cobs, fruit peels, straw to produce xanthan. Xanthan-based hydrogels can form in with the presence of cations, such as Mg_2^+, Pb_2^+ , Cd_2^+, or Ca_2^+ hydrogel based on xanthan gum are possible. Applications for xanthan as well as hydrogel polysaccharide can be found in a number of industries, including the food business and medical (such as tissue engineering and medication delivery systems). Anionic polysaccharide xanthan can combine with cationic chitosan to generate physical hydrogels. It

may be belived that xanthan-chitosan hydrogel will improve the nutritional values of probiotics that are encapsulated in both gastrointestinal and dairy storage conditions that mimic both ambient temperature and refrigerator storage. Two different single-layer bead types (xanthan–chitosan) and two-layer (chitosan–xanthan–xanthan) were made.[25]

Polymers	**Extracted from**	**Pharmaceutical properties**
Chitosan	Chitins	Ulcer healing , wound healing, antitumor, antioxidant
Carrageenan	Red sea weed	Antimicrobial ,immuomodulatory, anti-inflammatory, wound dressing,
Hyaluronic acid	Animal tissues like rooster comb's, cock's comb's	Tissue healing
Alginate	Marine brown algae	Wound dressing , tissue engineering
Xanthan	corn cobs , fruit peels	Tissue engineering , drug delivery system's

Preparation techniques of Hydrogel

Hydrogels are networks of polymers that exhibit hydrophilic properties. While water soluble monomers are commonly used for creation of hydrogels, water –resistant monomers are sometimes added to the hydrogel synthesis process to control the properties for specific uses.

Bulk polymerization

The most essential technique is bulk polymerization , which involves only monomers with monomer – soluble initiators. A substantial amount as well as rate of polymerization are caused by a high monomer concentration. Where as the reaction's viscosity is notably higher with conversions. As result of bulk polymerizing monomers to produce homogenous hydrogel is a clear, transparent along with highly stiff polymeric matrix. When submerged into water, the clear matrix expands and becomes smooth and versatile.[26]

Solution polymerization/cross-linking

Copolymerization with cross-linking in solution procces, ionic along with neutral monomers are combined with the multifunctional crosslinking solution. Polymerization is the process initiated by thermal initiators , such as UV

light or redox initiating systems. The inclusion of a solvent acts as a radiator of heat being an important benefit associated with solution polymerization. The generated hydrogels must be rinsed using water that was distilled to eliminate the initiator, easily soluble as well as accessible polymer, cross-linking substances, oligomers, monomers,also other contaminants. The phase separation takes place with a heterogenous hydrogel is produced when water is added at polymerization process, the water concentration becomes higher than that required for equilibrium swelling. Common solvents in cross-linking solution for hydrogels such as ethanol, water, bezyl alcohol, as well as mixture of the two. In this process the solvent can be removed from the hydrogels by swelling in the water once the gel has formed.[27]

Suspension polymerization or inverse-suspension polymerization

Suspension polymerization has become an helpful method while it eliminates need for grinding by producing goods in the form of powders or microspheres, or beads. The tearm "inverse suspension" refers to the polymerization process that occurs when water-in-oil(W/O) approach as chosen over most widely used oil-in-water(O/W) method. Throughout hydrocarbon phase, the initiator and monomers are distributed uniformly using this technique

The kind of dispersant, rotor design, agitation speed, along with thickness of solution containing monomer are the main parameters affecting size and shape of the adhesive particles. Several in-depth publications have already been written about hetero-phase polymerizations. The dispersion requires regular stirring in addition to a lower hydrophilic-lipophilic balance(HLB) immersing agent because of its thermodynamic instability.[26,27]

Grafting to a support

The bulk process of polymerization - produced hydrogels frequently exhibit brittle structures by design. To improve hydrogel's mechanical properties, it can be surface coated and grafted into a more robust support. By employing this technique, free radicals are able to directly polymerize monomers onto a stronger support surface, forming a network of covalent interactions among the monomer and the support. Hydrogel has synthesized by various polymeric supports using the grafting technique.[28]

Polymerization by irradiation

To create hydrogels of the unsaturated molecules, ionizing high energy radiation has been employed as an initiator, like electron beams along with gamma rays. Radiation supplied to an water based polymeric solution, radicals develop on the polymeric strands. Furthermore, radioactivity of water molecules yields l radicals of hydroxyl. After attacking chains of polymer, these radicals develop into macro-radicals.[29]

Eventually , the macro-radicals recombine on various networks to form covalent bonds, results in the creation of cross-linked groups. Crosslinking polymeric compounds like vinyl alcohol, ethylene glycol, and acrylic acid is produced with radiation method. The fundamental benifit of radiation acceptance beyond chemical initiation in production of Hydrogels that are resposibily pure and initiator –free.[30]

Evaluation and Characterization of Hydrogels

a) Visual appearance of formulation

The color, force of adhesion, consistency, stickiness, the hydrogel transparency, clarity and texture existence of any kind of grit were all evaluated.[31]

b) pH Determination

With a digital pH meter, the pH for hydrogel formulation measured. One gram of hydrogel is dissolved in 10 milliliters of distilled water, the mixture was allowed for two hours. The pH of hydraulic gel measured.[31]

c) Spreadability Test

The two watch glasses were used to calculate spreadability. The hydrogel was added into the watch glass in an amount of 500mg, and it was held there for some time. After positioning the second watch glass 5 cm above the hydrogel, the spreadability was determined. The force used and the amount of gel that spread across the glass were used to gauge the spreadability. The measurement unit is g/cm/sec.[32]

d) Homogeneity

After the gels were placed within the container, optical examination was used to check the homogeneity of each hydrogel preparation. They were examined to see if any aggregates were present and how they looked.[32,36]

e) Viscosity

The viscosity was measured using the Brookfield (DV-III) viscometer. Hydrogel was put into container then fourth spindle is added, owing for the formulation's with greater viscosity. Next, each hydrogel's viscosity was determined at 25℃ and 50-250RPM.[33,36]

f) Gel strength

Gel durability was measured in seconds, the weights soak-in time was used to determine the gels strength. A hydrogel composition weighing 5 grams was encased by a 3.5 gram weight. The durability of the gel is measured through the number of seconds required for its weight that pass through 0.5cm of gel.[34]

g) Stability Studies

For a period of 28 days, the six hydrogel compositions were stored in polyethylene boxes between 2° and 8° C. Following this, the hydrogel samples were examined visually for formulation look and tested for physical and chemical stability (pH, API concentration), as well as colour, texture, and viscosity.[35]

h) Drug content

The formulation (1g) was dissolved for at least 30 minutes in 20ml of phosphate buffer saline in order to extract the drug content. The mixture was filtered by using a Whatman filter paper. Then filtrate was again diluted by 10 milliliters of buffer solution,then UV-VIS spectrophotometer been used to measure the mixture's absorbance at 348 nm.[37]

i) Percentage yield

After weighing the empty container holding the hydrogel, then weighing the container containing the hydrogel. For determination of the practical yield reduce total mass for the container that is empty from the final weight of the container filled with the gel. After that the following formula was used to get the % yield:

(Practical yield/Theoretical yield) x 100 = Percentage yield

j) *In-vitro* drug release

With the Franz diffusion cell device, investigations for *in-vitro* release of drug were carried out. Little amount of the hydrogel was obtained and placed on the membrane that is attached to the receiver. To ensure that the phosphate buffer was heated to the physiological temperature, each receiver was filled with it and fixed with a magnetic stirrer measuring pH 6.8. Following that, the medication comes into touch with the buffer and dissolves there. By using a UV-Vis spectrophotometer, value of absorbance was measured at 348nm for a period of six hours following the removal of 1 milliliter of the buffer. When the medication is taken out of circulation, the same quantity of buffer is changed out every hour. The concentration and drug release were measured in in-vitro tests, and the results were expressed as a percentage.[38,39]

Conclusion

An essential step in the creation of a formulation is the selection of the polysaccharide that will make up the polymer matrix, as this will determine the formulation's spreadability and gelling strength. In this work, effectiveness of probiotic hydrogels using various polysaccharides and demonstrated their excellent therapeutic qualities and durability. This review concluded that probiotic material can come into longer contact with the

skin due to the polysaccharide composition, which improves penetration. Therefore, it is reasonable to assume that formulations containing polysaccharides will have a greater therapeutic impact when applied to the affected skin.

Future Aspects

The enormous progress reflects the tremendous study of hydrogels for therapeutic distribution that have occurred during the previous 50 years. Through that time, Hydrogels have been evolved from relatively simple networks of chemical, physical cross-linking to an extended release of one component to modern sophisticated multifunctional systems able to releasing multiple therapeutics in the controlled and triggering with both space and time. We offer an overview of the fundamental requirements that are now in place for a hydrogel system that can effectively and efficiently encapsulate and distribute medicines.[40]

While each therapeutic hydrogel's design should be specific to the conditions it is intended to treat, the ability for polysaccharide formation can be thought of as an important requirement. Depending on the crosslnking mechanism employed, for chemical cross-linking also a rapid as well as significant responsiveness for environment or physical gelation triggering(noncovalent cross-linking) is seen necessary in this regard. A second fundamental need is that every medication must be administered at the recommended dosage at particular stages of the therapeutic regimen. Even while the very basic hydrogels that have been produced may also deliver .Many of the novel ideas covered in this Perspective from the 20th century permit the control of the release following hydrogel administration, offering improved control to sustain an ideal drug concentration throughout time. We think the new ideas, as presented in this Point of View, will greatly enhance the performance, safety, and applicability of medicinal hydrogels and, consequently, expand their function in the field of therapeutic delivery.[40]

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