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A review on Starch- based hydrogel as a carrier of wound healing medicated product

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Abstract:

Now a day millions peoples are suffered from acute and chronic skin injury every year. India has the 10th rank in mortality due to the road accident. The management of wound care has been changed from past few years and in current scenario modern dressing improve wound healing by handling wound fluid in a way that prevents accumulation of excess exudates. A hydrogels can be defined on the basis of chemical or physical cross-linking of individual polymer chains, a hydrogel is made up of three- dimensional network of hydrophilic polymers that can be swell in water and hold a lot of water. The network of hydrogel is hydrophilic due the presence of hydrophilic groups like NH, -COOH, -OH, -$CONH_2$, -CONH -, and -SO_3 H. Natural and synthetic polymers are used in manufacturing of hydrogels. Hydrogels havemany applications in biomedical field like drug carriers,contact lenses, artificial corneas, wound dressings, coatings for sutures, catheters, and electrode sensors. In this review article, we are highlighted starch-based hydrogels, advantages, disadvantages, classification, preparation and application with some commercially available hydrogels worldwide.

Keywords: Hydrogels, Amylase, amylopectin, Cross-linked hydrogel, pH measurement, Biomedical application and Commercial products.

I Introduction:

Around 37 million people worldwide encounter chronic wounds every year, and millions more suffer from both acute and chronic skin injuries every year [1].India has the tenth-highest global death rate from road accidents.This has an impact on the nation's economy in addition to the quality of each patient's life.The goal of wound care has changed over the past 50 years from drying out the wound bed to maintaining a balanced wet environment [2].Modern dressings, which aim to improve healing by handling wound fluid in a way that prevents accumulation of excess exudate while maintaining a certain degree of moisture, have largely replaced traditional dressings, which served the primary purpose of absorbing wound exudate and caused crust to form on the wound surface with noticeable scarring [3].Due to the chemical or physical cross-linking of individual polymer chains," a hydrogel is a three-dimensional (3D) network of hydrophilic polymers that can swell in water and hold a lot of water while keeping the structure". It was first introduced byWichterle and Lím in1960 [4].For a substance to be considered a hydrogel, water must, by definition, make up at least 10% of the total weight (or volume).Due to their high water content, hydrogels also have a degree of elasticity that is extremely close to that of genuine tissue.The network of hydrogel is hydrophilic because it contains hydrophilic groups like -NH, -COOH, -OH, $-CONH_2$, -CONH -, and $-SO_3$ H. Natural and synthetic materials are used in preparation of hydrogel.The ability of hydrogels to retain a significant amount of solvent (such as water or biological fluids) under various circumstances is its distinguishing characteristic.Hydrogels are flexible and squishy, similar to living tissue, which makes them an excellent material for a wide range of possible applications [5]. Synthetic polymers are mainly used tomanufacture hydrogels

that are currently found in the market because they exhibit some exceptional mechanical, physical and chemical characteristics.They also have some shortcomings.They are unsustainable, difficult to biodegrade, and their production is not cost-effective or renewable [6].For these reasons, researchers are paying increased attention to hydrogels made from naturally occurring polysaccharides such starch and cellulose [7-8].Due to its simplicity in manufacture and self-application in clinical and basic applications, hydrogels have been widely exploited as drug carriers.Contact lenses, artificial corneas, wound dressings, coatings for sutures, catheters, and electrode sensors are just a few of the biomedical applications of hydrogels [9].

Advantages of starch- based hydrogel:

Some advantages of starch- based hydrogels are as follows [10].

1. It is abundant in nature and easily found over the world.
2. Starch based hydrogels are affordable and attractive.
3. Preparation method of starch- based hydrogels is easier than other methods.
4. It is eco-friendly in nature.
5. Starch based hydrogel have maximum absorption capacity of solvent.
6. It can use in different processes.

Disadvantages of starch- based hydrogels:

Starch based hydrogels have some disadvantages with advantages which are listed below [11].

1. It has low surface area.
2. Chemical derivatization is required to increase the sorption capacity.
3. It has poor durability.

Starch characteristics and structure:

It is polysaccharides. In the structure of starch, α-D (1-4) and α-D (1-6) links hold monosaccharides (glucose units) together [12–14].Two forms of polysaccharides, amylose and amylopectin, make up the majority of the starch structure and account for 98–99% of its dry weight [15, 16]. The structure of amylopectin and amylase differ from each other due to the differences found in their molecular weight.While amylopectin is made up of branching linkage,and amylose has a linear structure [13, 15].The structure of starch shown in figure 1 and figure 2. The sources of the starch (potato, wheat, or maize) and the crystallinity of the polysaccharides are the two key determinants of the amount of amylose and amylopectin present in starch [17].In starch, there are roughly 70% amorphous and 30% crystalline mass, respectively [18].Amylose is highly soluble in water and forms a helical shape [25].The primary cause of starch granules' hydrophilic property and strong intermolecular attraction is the hydrogen bonds formed by the -OH groups on their surfaces [19, 16].These -OH groups have a significant impact on the reactivity of starch.Hydrogen bonds, esters, and ethers can occur when starch is oxidised or reduced [20].

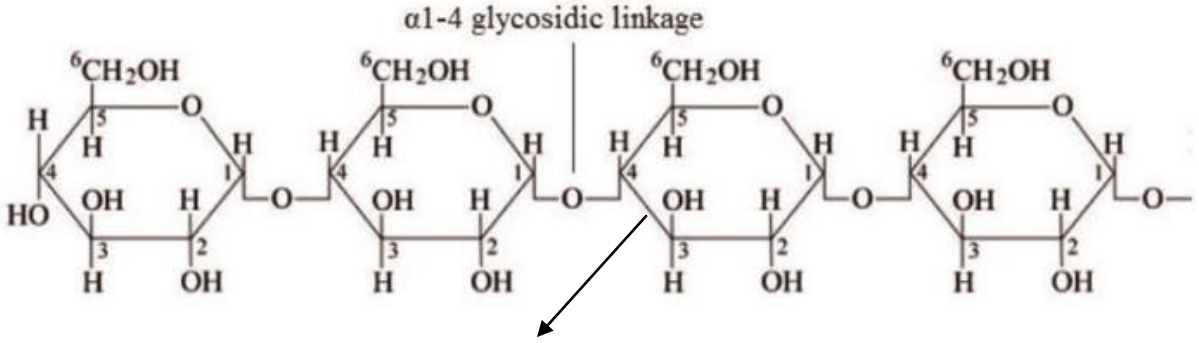

Figure 1. Structure of amylase

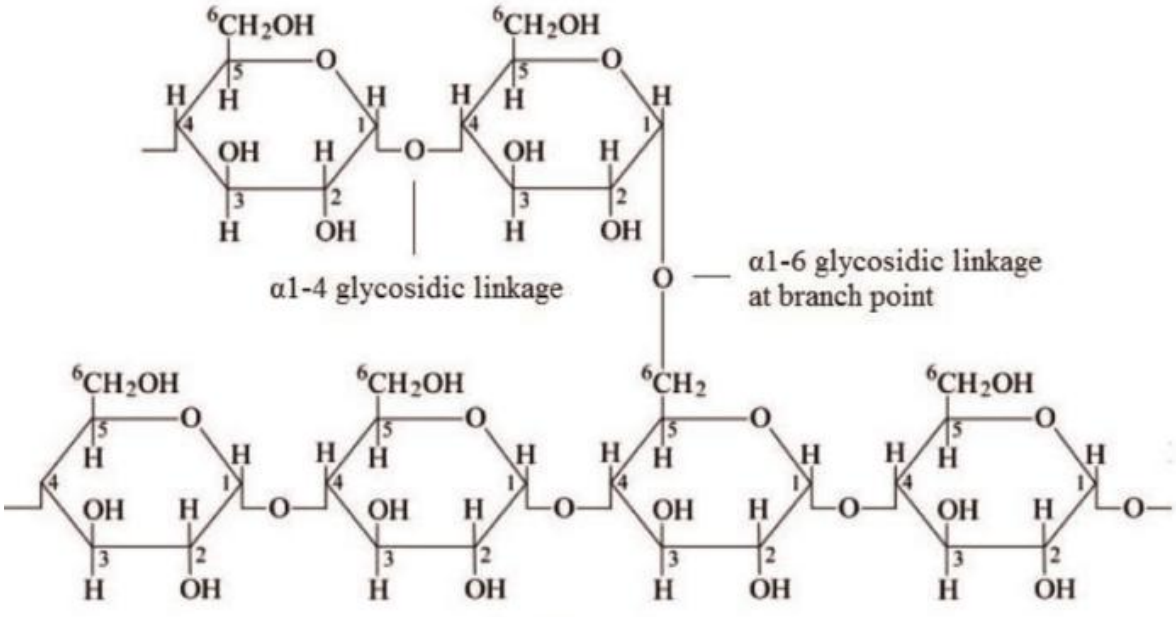

Figure 2. Structure of amylopectin

Classification of hydrogel:

Hydrogels are classified as on the following basis.

1. ***On the basis of nature of the cross-linked junction:***

   On the basis of nature of cross linked junction hydrogels are classified as follows (figure 3).

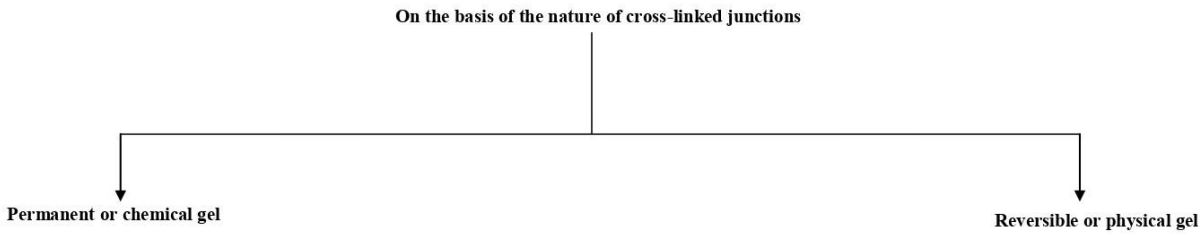

Figure 3. Classification of hydrogel on the basis of nature of cross-linked junction

   a. Permanent or chemical gel:

It is called permanent or chemical gel because these are covalently cross-linked networks.They reach an equilibrium swelling condition that is determined by the crosslink density and the polymer-water interaction parameter. For example,dextrans functionalized with vinyl sulfone are cross-linked with thiolated PEG [21].

b. ***Reversible or physical gel:***

When the networks are held together by molecular entanglements, and/or secondary forces such as ionic, hydrogen bonding, or hydrophobic contacts, they are referred to be reversible' or physical' gels.Physical interactions between various polymer chains in physically cross-linked gels inhibit disintegration.All of these interactions are reversible and susceptible to disruption by stress or alterations in the physical conditions. For example, formation of reversible hydrogel between α-cyclodextrins and PEO polymers [21-23].

2. On the basis of origin:

On the basis of origin hydrogels are classified as follows (Figure 4).

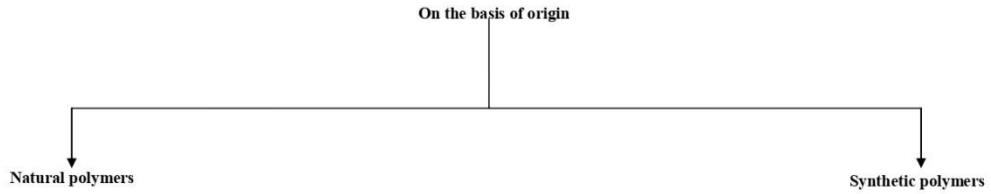

Figure 4. Classification of hydrogel on the basis of origin

a. Natural polymers:

These polymers are biodegradable, biocompatible and they support celluar activities. It does not have enough mechanical characteristics.Examples include

polysaccharides like alginate and agarose, as well as proteins like gelatin and collagen [21].

b. Synthetic polymers:

Absence of inherent bioactive characteristics. Examples of acrylic acid include methacrylic acid, vinyl acetate (MAA), and hydroxyethyl methacrylate (HEMA) [21].

3. On the basis of preparations:

On the basis of preparations hydrogels are classified as follows (Figure 5).

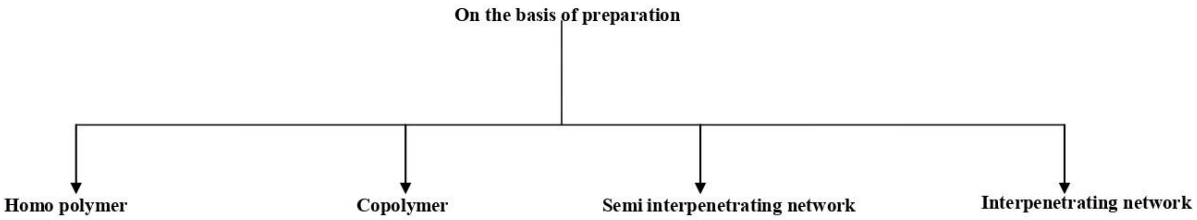

Figure 5. Classification of hydrogels on the basis of preparation [24].

a. Homo polymer:

Homo polymers are networks of polymers made from just one type of monomer.It is the fundamental structural component of any polymer network.Depending on the type of monomer used and the polymerization process, homo polymers may have a cross-linked skeletal structure.Contact lenses and drug delivery systems both use cross-linked homo polymers. [25]

b. Copolymer:

Copolymeric hydrogels are made up of two or more different species of monomers with at least one hydrophilic component which organized randomly, in blocks or alternately throughout the polymer network chain **[26]**

c. Semi interpenetrating network:

Semi-inter penetrating networks are created when one linear polymer pierces another cross-linked network without the use of any additional chemical bonds.[27]

d. Interpenetrating network:

IPNs are generally understood to be the intimate conjunction of two polymers, at least one of which is created or linked in close proximity to the other.[28]This is commonly accomplished by dipping a hydrogel that has already been polymerized into a mixture of monomers and a polymerization catalyst.Due to the persistent interconnecting of network segments, IPN can get around thermodynamic incompatibility and only obtain limited phase separation.The fundamental benefit of IPNs is the ability to create relatively dense hydrogel matrices that have stronger, stiffer mechanical properties, controlled physical properties, and more effective drug loading than other hydrogels.[24]

Hydrogel preparation methods:

The various preparation methods are used for hydrogel such as physical cross linking, grfting polymerization, chemical cross linking and radiation cross linking. These methods can enhance mechanical characteristics viscoelasticity for application in the biomedical and pharmaceutical areas.[29] These methods are as follows.

1. Physical cross-linking:

Physical or reversible gels have gained popularity because of their relatively simple manufacture and the benefit of not requiring cross-linking agents.The integrity of the substances to be entrapped (such as cells, proteins, etc.) and the requirement for their removal prior to application are both impacted by these agents.The following are the numerous techniques listed in the literature for making physically cross-linked hydrogels.

a. Heating / cooling polymer solution:

Helix formation, helix association, and junction zone formation are all responsible for the gel's formation.Carrageenan is found as a random coil shape in hot solutions above the melting transition temperature.It becomes hard helical rods as it cools.In the presence of salt (K+, Na+, etc.), double helices further assemble to form stable gels as a result of the sulphonic group's (SO-3) screening repulsion (Figure 1).Examples include polyethylene oxide. polyethylene glycol, polypropylene oxide, and polylactic acid hydrogel. [30]

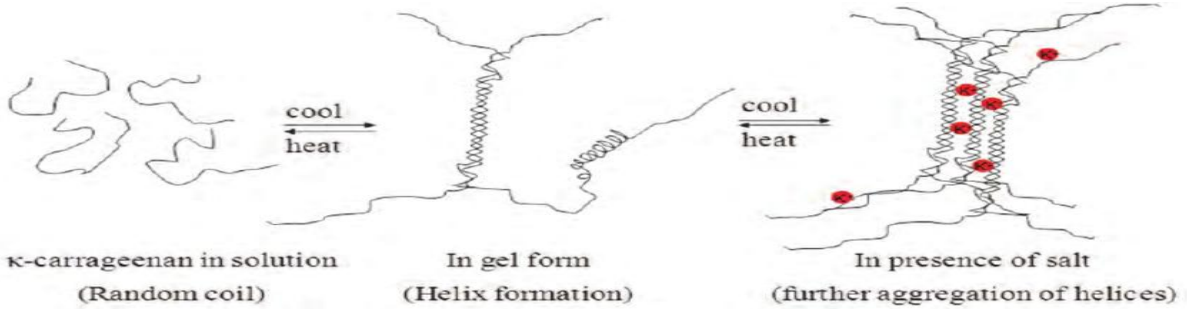

Figure 6. Gel formation due to the aggregation of helix upon cooling a hot solution of carragenan [23]

b. *Complex coacervation*:

It can be prepared by the mixing of a polycation with polyanion.According on the concentration and pH of the corresponding solutions, polymers with opposite charges will cling together and form soluble or insoluble complexes.Coacervating polyanionic xanthan with polycationic chitosan is one such instance. Positively charged proteins that are below their isoelectric point are more likely to bind with anionic hydrocolloids and create polyion complex hydrogels.[31]

c. Ionic interaction:

Di- or tri-valent counterions can be used to cross-link ionic polymers.The idea behind gelling a polyelectrolyte solution (like Na^+ alginate$^-$) with a multivalent ion of opposite charges (like Ca^{2+} + $2Cl^-$) is based on this technique.Other examples are chitosan-glycerol phosphate salt, chitosan-polylysine, and chitosan-dextran hydrogels. [23]

2. Chemical cross-linking:

In chemical cross-linking, monomers are grafted onto the polymer's backbone or two polymer chains are joined together by a cross-linking agent.Natural and synthetic polymers can be cross-linked by reacting with cross-linkers like aldehydes to produce their functional groups, such as OH, COOH, and NH_2 (e.g. glutaraldehyde, adipic acid dihydrazide).The cross-linked hydrogel has been produced using cross-linkers including glutaraldehyde and epichlorohydrin, among others.A good illustration of this is hydrogel, which is made by crosslinking maize starch and polyvinyl alcohol with glutaraldehyde.Using epichlorohydrin as a cross-linker and cellulose in NaOH/urea aqueous solutions as a starting material, hydrogels can also be made by heating and freezing the material. [32]

3. Grafting cross-linking:

Hydrogels created by bulk polymerization typically have a weak structural foundation.A hydrogel can be surface-coated onto a more durable support to enhance its mechanical qualities.Using this method, a chain of monomers is covalently bound to the support by first creating free radicals on a surface that is stronger than the support and then polymerizing monomers directly onto it.By using grafting methods, hydrogel has been

created on a variety of polymeric supports.An illustration of this method is the use of N-vinyl-2-pyrrolidone to graft acrylic acid onto starch. [33]

4. ***Polymerization through irradiation:***

Unsaturated compound hydrogels have been prepared using gamma rays and electron beams, two types of ionising high energy radiation.Examples are poly (ethylene glycol), poly (vinyl alcohol), and poly (acrylic acid)

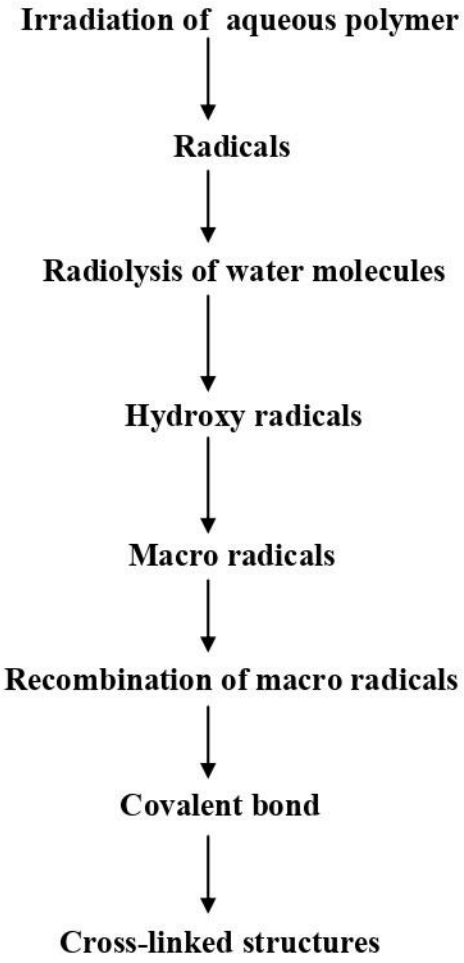

Figure 7. Layout of cross-linked hydrogel preparation method by polymerization through irradiation.[9]

Evaluation test for hydrogels:

The physical, rheological, and antifungal activities of the hydrogel formulations are investigated. Skin irritation test carryout only in the case of topical formulation. Some important evaluation test for hydrogels are as follows.

Homogenesity: The hydrogels are tested for their physical characteristics like clarity, colour and phase separation by visual inspection. These are investigated for the presence of any aggregates.[34]

Grittiness:Microscopically, any particulate matter in the formulations is detected. This phenomena is known as Grittiness.[35]

pH measurement: The pH of hydrogels are determined by using digital pH meter. 1 gram of hydrogel is dissolve in 100 ml of distilled water and keep it for two hours.Each formulation's pH is measured three times, with the average readings being computed and reported.[36]

Spreadability:On graph paper, concentric circles of varying radii are formed, and a glass plate is fastened to each of them.On the lower plate's centre, 5gms of gel are deposited. 100 gram hydrogel placed on another galss plate and after 1 minute spread diameter is recorded.[37]

Extrudability:The hydrogels are filled into collapsible tube.The weight required in grammes to extrude a 0.5 cm ribbon of gel in 10 seconds is used to gauge the extrudability of gel formulations after they have been established in the containers.[38]

Drug content: In 100 ml of phosphate buffer with a pH of 5.8, 1 gram of hydrogel is dissolved.With the aid of phosphate buffer of pH5.8, suitable dilutions are created.Using a UV spectrophotometer, absorbance is measured at 282 max nm.[39]

In-vitro drug diffusion study: In-vitro drug release is carried out by Franz diffusion cells. 0.5 gram of hydrogel is incorporated on the surface of cellophane membrane which act as a donor compartment.The receptor compartment is filled with phosphate buffer pH 5.8 as the dissolving media.The entire system is set up on a magnetic stirrer with the thermostat set to 37 °C.Samples are taken on a regular basis, and sink conditions are kept consistent by changing the old buffer solution.A UV spectrophotometer is used to evaluate the samples after collection at 282 nm.[40]

Skin irritation test: Skin irritation test is performed on ten healthy volunteers (male and female). 100 mg hydrogel spread over the skin surface about 2 square cm of area and after that observe the any lesion, irritation or redness.[41]

Starch-based formulation of hydrogel:

Pagano et al., formulated starch-based sustainable hydrogel which was loaded with saffron petal extract (crocus sativus) for the wound healing. They were carried out two different extraction method using freeze dried crocus sativus petal/ extraction solvent in ratio 2.46 gm/ 200 ml.The composition of the extract supported on starch powder particles were optimised starting from the "glycerol gel (starch glycerolate)" and was then created as a gel.A mechanical stirrer fitted with a three-blade helical impeller was used to mix the corn starch powder (9.960% w/w) in a solution of bidistilled water (20.000% w/w) and glycerol (70.000% w/w) until gelification.After allowing the gel to cool, saffron extract (0.045% w/w) was added while being mechanically stirred (500 rpm, 5 min).[43]

Zang et al., prepared xanthum gum/ starch-based hydrogel by using a therapeutic agent called honeysuckle a Chinese medicine for the treatment of intestinal inflammation.[43] Abdul khalil et al extracted patchouli essential oil from dried leaves of pogostemon cabin and formulated a

starch-based hydrogel which was loaded with patchouli essential oil and used it as anti-microbial formulation.[44]Mojally et al., prepared hydrogel films from corn starch, polyvinyl alcohol, castor oil and silver nanoparticles biosynthesized from Mentha piperita leaves extract and used it as wound healing dressing.[45]Koev et al., developed colon specific starch hydrogel which composed of vanillin, 5-fluorouracil and doxorubicin drugs for the treatment of ulcerative colitis.[46] Abou El- Naga et al., formulated starch-based hydrogel nanoparticles loaded with bisphenol (Moringa oleifera leaf extract) and it showed a hepatoprotective activity.[47]Delavari et al., developed a starch- based hydrogel composite film consist of polyvinyl alcohol for the wound healing dressing.[48] Abdollahi et al., developed a bioactive carboxymethyl starch-based hydrogels loaded with CuO nanoparticles and used it as a antimicrobial agent.[49] Mala and Anal et al., formulated pectin- resistant starch-based hydrogel beads loaded with bromelain for removing dead cells of burning skin.[50] Hanafy et al., prepared starch-based hydrogel nanoparticles (NPs) loaded by anthocyanins for the treatment of glycogen storage at cardiomyopathy.[51]

Table 1. Various formulation of starch-based hydrogel

Sr. no.	Formulation name	Therapeutic agent	Therapeutic use	References
1	Starch-based sustainable hydrogel	Crocus sativus petal extract	For wound healing	[42]
2	Xanthum gum/ starch-based hydrogel for controlled release	Honeysuckle (Chinese medicine)	Treat intestinal inflammation	[43]
3	Starch-based hydrogel loaded with patchouli essential oil	Patchouli (pogostemon cabin) essential oil	Anti-microbial purpose	[44]
4	Polyvinyl alcohol/ corn starch/ castor oil hydrogel films loaded with silver nanoparticles	Silver nanoparticles	Wound dressing	[45]

5	Starch hydrogels as targeted colonic drug delivery vehicles	Vanillin, 5-fluorouracil and Doxorubicin	Treatment of ulcerative colitis	[46]
6	Starch- based hydrogel nanoparticles loaded with polyphenolic compound	Bisphenol (Moringa oleifera leaf extract)	Hepatoprotective activity	[47]
7	Starch-based hydrogel composite film	Poly vinyl alcohol	Anti-bacterial	[48]
8	Bioactive carboxymethyl starch-based hydrogels	CuO nanoparticles	Antimicrobial	[49]
9	Pectin-Resistant starch-based hydrogel beads	Bromelain	Anti-inflammatory agent	[50]
10	Starch-based hyderogel NPs Loaded by Anthocyanins	Anthocyanins	Treat glycogen storage at cardiomyopathy	[51]

Pharmaceutical application of Hydrogels:

Hydrogels are have following applications in the field of pharmaceutical sector.

1. ***Drug delivery in the oral cavity:***

   The local treatment of oral disorders such periodontal disease, stomatitis, fungal and viral infections, and oral cavity malignancies can benefit greatly from drug administration to the oral cavity.For instance, a bioadhesive tablet has been created and is marketed under the name **Aftachw**.This product is made up of two layers: a lactose-free, non-adhesive backing layer and a bioadhesive layer comprised of hydroxypropyl cellulose and poly (acrylic acid).It is a method for administering triamcinolone acetonide locally to treat ulcers.[52]

2. ***Drug delivery in GI tract:***

   The ability to administer medications for compliance therapy and its huge surface area for systemic absorption make the GI tract without a doubt the most common route for drug delivery.Drugs can be delivered locally to particular areas in the GI tract using hydrogel-based devices, just like buccal delivery.For instance, stomach-specific antibiotic

drug delivery devices for peptic ulcer disease therapy of Helicobacter pylori infection.They created cationic hydrogels with pH-sensitive swelling and drug release capabilities for targeted antibiotic delivery in the stomach's acidic environment.[53]Recently, it was revealed that oral insulin delivery using pH-responsive complexation hydrogels.The PMAA copolymers with graft chains of polyethylene glycol were employed to cross-link the hydrogels that were used to shield the insulin in the harsh, acidic environment of the stomach before releasing the medication in the small intestine.[54]

3. **Rectal delivery:**

Numerous different drug kinds have been administered via the rectal route for the local treatment of illnesses such as haemorrhoids.This route is more practical since it avoids first pass metabolism and allows medications absorbed from the lower region of the rectum to enter the bloodstream directly.Since conventional suppositories are solid at room temperature and melt or soften at body temperature, they are modified for rectal delivery.Drugs released from conventional suppositories in an unregulated manner make it difficult for them to be adequately held at a specific location in the rectum, and they may migrate upward to the colon.This frequently causes the bioavailability of particular medications to vary.If they are made to demonstrate a strong enough bioadhesive property after being administered via rectal route, hydrogels may provide a useful solution to the issue with conventional suppositories in this situation.For instance, polycarbophil and sodium alginate produced the greatest muco-adhesive force and the least amount of intra-rectal migration to the suppositories among the muco-adhesive

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polymeric compounds evaluated, resulting in the greatest bioavailability of propranolol.[55]

4. **Occular delivery:**

The medications administered demonstrate limited absorption and the traditional ophthalmic preparations, like eye drops, have a tendency to be quickly removed from the eye, which results in poor ocular bioavailability.Furthermore, due to their short-term retention, regular dosage is frequently required to maintain therapeutic efficacy for a considerable amount of time.These difficulties have spurred researchers to create drug delivery devices that extend the duration of medicines' ocular residency period.Some dosage forms, such suspensions and ointments, can be kept in the eye, albeit due to the properties of solids and semi-solids, these might occasionally make patients feel uncomfortable.Because of their elastic qualities, hydrogels can also serve as an eye drainage-resistant device, which may provide patients with a better feeling and less grit.Particularly because of their ease in dosing as a liquid and their long-term retention property as a gel following dosing, in-situ-forming hydrogels are appealing as an ocular medication delivery strategy.. For the ocular delivery of pilocarpine, for instance, an in-situ-gelling system of alginate with high guluronic acid concentrations.[56]

5. **Wound healing:**

Hydrogels, which are cross-linked materials with the capacity to store both water and drugs, can hold and maintain wound exudates because of their capacity to hold water.Hydrogels made of gelatin and sodium alginate can be used to cover and shield a wound against bacterial infection.[57]

6. **Hydrogels for trandermal drug delivery system:**

When used topically, hydrogels have various benefits, including the capacity to circumvent hepatic metabolism, which boosts drug bioavailability and effectiveness.To provide a consistent drug release, transdermal drug delivery systems are employed.Hydrogels can be removed more easily than other dose forms like patches and ointments because they are swollen and mimic live tissues.Gentamycin-containing new hydrogels based on poloxamer 407 are more effective at treating skin infections than gentamycin administered orally, which can have major side effects.[58,59]

Some marketed products of hydrogels are listed in table no.2.

Table 2. Some marketed product of hydrogels in form of wound dressing

Sr. no.	**Product name**	**Manufacturer name**	**Hydrogel composition**	**Application**	**References**
1	AquaDerm™	DermaRite industries	2-Acrylamido-2 methyl-1 propanesulfonic acid sodium, propylene glycol, poly (ethylene glycol) dimethacrylate, and 2-hydroxy-2-methylpropiophenone with 38–55% water make up the hydrogel sheet.	Minor burns, radiation tissue damage, and pressure ulcers	[62]
2	Suprasorb® G	Lohmann &Rauscher Global	Acrylic polymer, polyethylene, and phenoxyethanol hydrogel film with a 70% water content.	first- and second-degree burns, scalds, lower leg ulcers, dry wounds, and pressure ulcers	[60]
3	Neoheal® Hydrogel	Kikgel	PEG, polyvinylopyrrolidon	Burns, bed sores,	[63]

			e, and agar are used to make the hydrogel sheet, which is crosslinked using electron beams. Contains 90% water content.	ulcers, abrasions, and other chronic wounds	
4	DermaGauze™	DermaRite industries	Acrylic polymer	Partial and full thickness wounds that are acute or chronic	[61]
5	Restore Hydrogel	Hollister Incorporated	Hyaluronic acid is present in hydrogel impregnated gauze pads, which aid in the autolytic debridement of wounds.	Partial and Full thickness wound	[64]
6	Simpurity™ Hydrogel	Safe n simple	Polyethylene oxide, polyvinyl alcohol, acrylate, polyurethane, and purified water-containing absorbent sheets	Dry scabs, skin burns, and open wounds	[65]

Conclusion:

Hydrogels made of starch have a variety of advantageous qualities.They are non-toxic, hydrophilic, biodegradable, and biocompatible. They also respond to pH.They are also affordable and easily accessible from natural sources, which makes them more desirable and intelligent polymer materials.Starch-based sustainable hydrogels can replace petroleum-based polymeric materials because of their eco-friendly nature.People won't be as dependable when it comes to synthetic polymers.The procedures used to prepare and

characterise starch-based hydrogels are considerably simpler.Although starch-based hydrogels have significant limitations, such as lower sustainability and inferior mechanical qualities, there are a growing number of intriguing applications for starch-based hydrogels.In the fields of agriculture, biomedicine (such as tissue engineering, drug delivery), water recycling, and the food industry, they are taking the place of synthetic hydrogels. In this review, a brief summarization of classification, preparation methods, evaluation methods for hydrogels and several applications in the field of pharmaceutical sector along with some commercial products of starch-based hydrogels are given.The researchers working in this field could benefit from this review.

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