REVIEW ARTICLE

Hydrogel Beads- A Versatile Dimension in Controlled Oral Delivery

Umesh K. Singh*, Preethi Sudheer

[1*]Department of Pharmaceutics, Krupanidhi College of Pharmacy, Bengaluru, Karnataka, India

Received: 14th June, 2022; Revised: 28th August, 2022; Accepted: 02nd September, 2022; Available Online: 25th September, 2022

ABSTRACT

Conventional oral dosage forms are the most preferred and convenient method to treat several diseases. However, the significant problem associated with these dosage forms is their inability to maintain constant therapeutic blood levels for a prolonged period due to inappropriate dosing, short half-life, first-pass metabolism, and poor absorption. All these factors lead to low bioavailability issues, patient inconvenience, especially from frequent dosing, and also local or systemic side effects. Therefore, much research has focused on controlled release delivery systems. Hydrogel beads are unique systems that use biopolymers as their skeleton. The distinctiveness of hydrogel bead systems such as their high-water holding capacity, swelling, and elastic nature paved their place in oral drug delivery systems. They can easily encapsulate and protect the active ingredients and enable prolonged and remotely programmed spatial and temporal drug release. This review is an insight into hydrogel beads, various polymers used in its preparation, their features and applications, and their advantages and disadvantages. This review highlights the advances in hydrogel beads as a drug delivery system.

Keywords: Beads, Controlled drug delivery, Cross-linking, Hydrogel, Ionotropic gelation.

International Journal of Drug Delivery Technology (2022); DOI: 10.25258/ijddt.12.3.88

How to cite this article: Singh, UK, Sudheer, P Hydrogel Beads- A Versatile Dimension in Controlled Oral Delivery. International Journal of Drug Delivery Technology. 2022;12(3):1453-1464.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

To acquire and preserve the optimal amount of drugs in the body, the precise supply of the drug from the delivery systems is a requirement that leads the adequate drug concentration at the site of action. For optimal therapy and drug side effect mitigation, various drug delivery strategies are employed. The oral route is one of the best routes, showing promise, and an efficient route for drug administration among the various routes due to numerous advantages such as ease of administration, therapy with a cheap cost, better bioavailability, formulation flexibility, and prolonged drug delivery.

Oral medication delivery methods account for roughly half of all drug delivery systems. The most extensively used dosage forms are oral controlled-release dose forms, although other drug delivery methods are in practice. According to patent literature and recent studies, there is an increasing focus on innovative formulations that stay in the gastrointestinal region for a long and reliable duration. The medication delivery system with gastro-retentive properties is a revolutionary method in this field.

Drugs with a short half-life and fast gastric emptying quickly leave the systemic circulation. There is a necessity of frequent dosing to achieve adequate therapeutic efficacy. Oral sustained-controlled-release dosage forms are being designed to counterpass the above-mentioned drawbacks that slowly release the medication into the stomach while maintaining an efficient amount of drug in the bloodstream for an extended period. The drug will be preserved in the abdomen and released in a regulated way after oral delivery, enabling the medication to be delivered consistently to its absorption location in the other parts of the gastrointestinal tract. Therefore a dosage form must be created that allows for prolonged stomach residence, which will allow for more time for medication absorption in the small intestine.[1-3]

Hydrogels are a 3D network of polymers and expand when exposed to water while preserving their mechanical strength. Hydrogels can store enormous volumes of water, similar to extracellular matrices. The hydrophilic functional groups connected to the polymer membrane provide hydrogels with their water-holding capacity, whereas cross-links among network chains give them stability to break down. Hydrogels are getting more popular due to their convenience of manufacture, the vast scope of applications, and high biocompatibility. Natural and synthetic hydrogels are cross-linked hydrophilic polymeric materials that can be either synthesized or commercialized. These polymers could be used in biomedical applications because they are suitable for human tissues. Compared to previous approaches in this

*Author for Correspondence: singhumesh5585@gmail.com

Table 1: Advantages and disadvantages of hydrogels

Advantages	*Disadvantages*
Compatible with living tissue, biodegradable, relatively non-toxic, flexible like normal tissues, and easy to modify.	Low tensile strength, therefore low load bearing capacity.
It can be administered via injection, and they can sense the alterations in the surroundings, including temperature, pH, or metabolite concentrations, and deliver their contents due to these alterations in the other direction.	It is challenging to fill hydrogels mostly with cells and drugs before cross-linking each of them in vitro like a premade matrix. The hydrogel provides a sensation due to the movement of the maggots.
The transport properties of the hydrogel are excellent. They can be used locally, allowing them to bypass the first-pass metabolism.	Hydrogel contact lenses can cause dryness, ischemia, lens accretion, and symptoms like a red-eye when worn as contact lenses.
As compared to conventional drug delivery systems, hydrogel targets particular areas such as the colon, and healing and growth hormones and other nutritional components are released at a specific moment.	Blood clotting at junction points and problems like medical surgery related to the insertion of the device and removal are further disadvantages.
They have a lower interaction with the drug, resulting in a more significant portion of the drug being released and more sustained and prolonged activity.	The hydrogel may require an additional dressing due to its non-adherent nature to keep them in place.
Reduced toxicity is one of the benefits of encasing microbial cells in hydrogel beads, thereby lowering adverse impacts while enhancing conformity at a lower cost.	Complex to manage, non-adherent, and has poor physicomechanical integrity, sterilization is complicating, cause clotting at junction areas, is therefore not suitable for wounds with substantial drainage, and requires a secondary dressing.

field, hydrogels in drug delivery provide various advantages, including sustainability and sensitivity without any side effects. Because of their well-established biocompatibility, hydrogels are frequently used as hosts (or vehicles to carry drugs) in drug delivery.[4]

Because of the structural similarity of hydrogels to the extracellular environment and their unique physicochemical and biological properties, they have been used for various biomedical applications, including tissue regeneration, biosensor membranes, and biomedical devices. Synthetic polymeric materials like polyacrylamide, Polyvinyl alcohol (PVA), Polyethylene glycol (PEG), polyacrylic acid, and naturally derived polymers like chitosan gelatin, poly alginate, and hyaluronic acid have been used to make a variety of hydrogels. Covalent bonds and physical bonding like ionic and hydrophobic interactions and hydrogen bonds are used to cross-link these polymers. Natural hydrogels are preferred because of their environmental friendliness, low production costs, biodegradability, and great raw ingredients.[5,6]

Hydrogel delivery technologies have found clinical use and can leverage therapeutically beneficial impacts of medication administration. Hydrogels can manage the delivery of various medicinal substances, macromolecular pharmaceuticals, tiny drug molecules, and cells concerning both spatial and temporal scales. Hydrogels create a basis for various physical and chemical interactions for the enclosed drugs to manage their release due to their controllable physical features, changeable degradation rate, and potential to preserve unstable compounds from deterioration.[7]

Hydrogel beads are one of the expansions of the hydrogel system. Beads are spherical objects that function as solid support for coating or encapsulating medicine in the beads' core. Beads can give controlled release. In addition, the bioavailability of medications formulated in beads has improved. Gastro-retentive beads address the problem of designing a gastro-retentive drug delivery method that maintains drug release and extends the dosage form's stomach residence until all medicines are released at the desired time.[8] Some of the advantages[9,10] and disadvantages[11] of hydrogels have shown in Table 1.

CLASSIFICATION OF HYDROGELS

A variety of hydrogel classifications and perspectives are presented in the literature. Hydrogels are classified as cationic, anionic, or neutral according to the ionic species on the bound units. As per the sources, hydrogels can be categorized into two types: those made of natural polymers and those made of synthetic polymers. Physical, chemical, and biological hydrogels are all possible. Physical hydrogels can change from fluid to gel due to changes in variables like temperature, ionic concentration, pH, and perhaps other circumstances like the combination of two components. Unlike other low-strength materials, chemical hydrogels rely on covalent bond formation to give biomechanical stability and resistance to deterioration. The gelation process in biochemical hydrogels is aided by biological agents and enzymes, and amino acids. Crystalline, semicrystalline, amorphous, and hydrocolloid clusters are some of the several types of hydrogels. Various type of classification is given in Figure 1.[12,13]

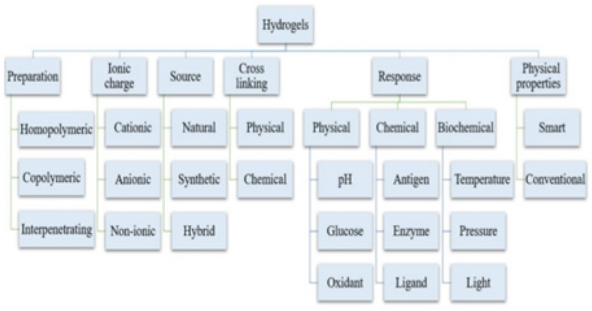

Figure 1: Classification of hydrogels on a different basis

Hydrogel Features

A hydrogel's most essential qualities are its tendency to store water and its permeability. Hydrogels have a comparable level of elasticity to human body's tissue because of high fluid amounts. The chemistry of a hydrogel can be changed by modifying its polarity, surface characteristics, expanding tendency, and mechanical characteristics. When polar hydrophilic groups come in contact with water it results in formation primary bound water. Thus, hydrophobic groups are exposed due to the expansion of the network, which could also interact directly with molecules of water, thereby leading to the formation of secondary bound water. The term "total bound water" refers to the sum of both primary and secondary bound water. Due to the water pressure of the polymer network toward unlimited dispersion, the network will hold more water; however, the physical cross-links will resist this extra swelling, resulting in a flexible network pullback force. "Free water/ bulk water" is the extra held water that is thought to occupy the gaps among the polymer network and the centres of bigger apertures, mesopore, or spaces.[14-16]

Biodegradable

The two determining factors for disintegration and dissolution of the hydrogel systems are the biodegradable nature of either the polymer chains or their structure. Biodegradable hydrogels with unstable connections are advantageous in cellular regeneration, injury repair, and drug distribution. The polymeric structure or the cross-links employed to make the hydrogel contain unstable connections. These unstable connections may be disrupted enzymatically or chemically under physiological conditions, with hydrolysis being the most prevalent mechanism. The maximum degradability is possible without creating hazardous substances due to decomposition.[14-16]

Biocompatibility

The hydrogel's biocompatibility is the third most essential distinctive quality. Biocompatibility refers to the hydrogel's immune system and the breakdown products it produces, which should not be hazardous. They should, ideally, be metabolized into innocuous compounds or eliminated through the filtration process in the kidneys. Hydrogels are more biocompatible than other materials primarily because of the presence of hydrophilic surfaces in contact with reduced interfacial free energy when interacting with physiological liquids, making them challenging for different proteins and cells to attach to them. Furthermore, because hydrogels are soft and rubbery, they cause minimal discomfort to the surrounding tissue. The cross-links among polymer matrices, which provide viscoelastic or proper elasticity, are responsible for the gel's structure (firmness), flexibility, and stickiness.[14-16]

MECHANISM OF DRUG RELEASE

Hydrogels' desired physical features, particularly their porous nature, bring significant benefits to therapeutic applications, including extended-release of drugs from dosage forms. Swelling, diffusion, chemicals, or other external factors can govern an appropriate release for a longer duration, as long as the active therapeutic material is kept at a relatively high concentration level.

In diffusion-controlled dosage forms with hydrogels, the release of the drug is controlled via diffusion through water-filled hydrogel apertures. The hydrogel layer is put atop the core made up of drugs in case of a reservoir drug delivery system, resulting in a large amount of drug in gel pills, spheres, or chunks at the core of the system, allowing for a steady rate of drug release.

The matrix approach uses polymeric apertures or pores to release drugs. However, the reservoir system produces a continuous and time-independent release of the drug. Time-dependent drug release occurs once the beginning release rate of the drug is related to that of the square root of time rather than remaining steady. Drugs are contained inside a transparent polymer that starts to swell while exposed to biological fluid, allowing for controlled drug release from hydrogels. The polymer network relaxes and swells above its boundary due to swelling, helping the drug to penetrate more easily. Because drug release can be closely regulated and non-specific adverse effects at non-target sites can be minimized, the release of drugs in response to environmental stimuli will be a suitable delivery approach. As a result, susceptive drug delivery devices have been developed that adapt to adjustments in pH, temperature, ionic strength, or glucose concentration and are therefore valuable for the treatment of disease conditions such as cancer and diabetes, which are described by local physiological changes that are particular to the disease's stages. By altering the polymer's composition, the hydrogel's sensitivity to the environment can be modified.

Hydrogels offer a broad array of clinical uses and significantly enhance the clinical result of medication delivery. The temporal and spatial delivery of tiny molecules, cells, and macromolecular medications has improved while hydrogels administer the drug. In recent years, continual research has been made to improve the design aspects of hydrogel beads

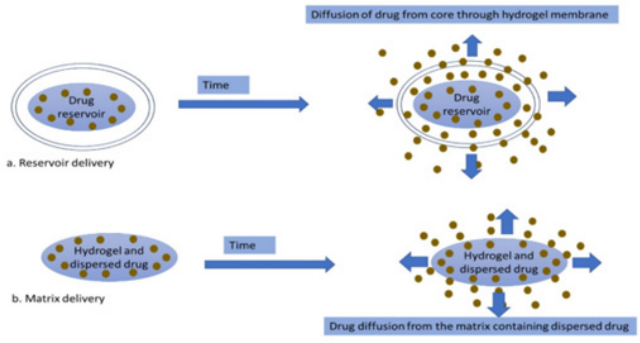

Figure 2: (a). Hydrogel layer coated drug core, in which concentration of the drug is more mostly in system's centre, allowing for a consistent release of drug in case of reservoir drug delivery system. **(b).** Matrix delivery facilitates a homogeneous dissolution rate or distribution throughout the three-dimensional shape of the hydrogel.

as they have been challenging to formulate for better drug distribution. These designs will help provide a better design that covers the formulation application in interpreting the clinical delivery and lipophilic drug delivery. Figure 2 shows the mechanism of drug release.[17,18]

PREPARATION AND CROSS-LINKING OF HYDROGEL BEADS

Natural and synthetic polymers have been intriguing for many pharmaceutical uses throughout the last decade. Natural polymers are more soluble, have no strength, and have lower heat stability than synthetic polymers. As a result, improving these qualities is critical for the extensive application of polymers. Synthetic cross-link polymers enhance the performance of these polymers without any doubt. Crosslinking polymers are divided into two categories: *in-situ* cross-linking and post-cross-linking. *in-situ* cross-linking occurs when a functional monomer is promptly cross-linked with a cross-linker to form a polymer's macromolecular chain, whereas post-cross-linking occurs after polymerization. Chemical, physical, and biological cross-linking are the three main types of cross-linking methods that have been extensively studied. Temperature, pressure, light, electricity, magnetic fields, stress, and pH changes can all be used to reverse physical and biological cross-linking. However, chemical cross-linking is irreversible.[19–27]

Physical Cross-linking

The various secondary forces involved in physical cross-linking are hydrophobic interaction, ionic forces, hydrogen bonding (intramolecular/intermolecular) contact, supramolecular chemistry, and stereo complexation. Different methods are available by which physical cross-linking can be achieved.[28–32]

Ionic interaction is the most potent and widely used physical cross-linking method as compared to other physical techniques. This ionic interaction is the most useful method to cross-link the hydrogel at room temperature under physiological or moderate conditions. Polyurethane cross-linking, like the ionic interaction that links alginate and pectin, is a frequent form of polymer cross-linking. Calcium ions are biocompatible as well as they can easily produce gelation, therefore, they are used to cross-link the alginate. This alginate hydrogel has a wide range of applications like drug delivery, lesion healing, scaffold for living cell encapsulation, and tissue regeneration. A key advantage of this approach is its capacity to manufacture long-lasting hydrogels at physiological temperatures and pH levels. Ca-ions are divalent cations and when these cations are attached to L-guluronic acid groups leading to the production of insoluble hydrogel networks along with dimerizing junctions by interacting with other polymer chains. The guluronic acid blocks of alginate chains pile up as a result of gelation or cross-linking. Furthermore, active substances are encapsulated and stabilized in gel microparticles by mixing a sodium alginate

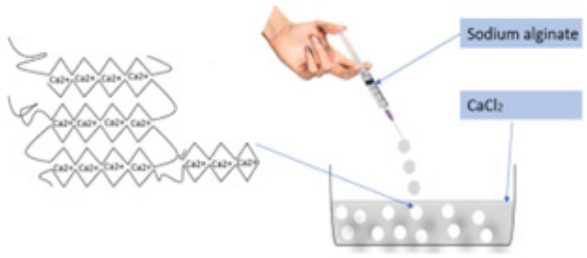

Figure 3: In an egg-box model, calcium ions gelate homopolymeric units of the -L-guluronic acid junction.

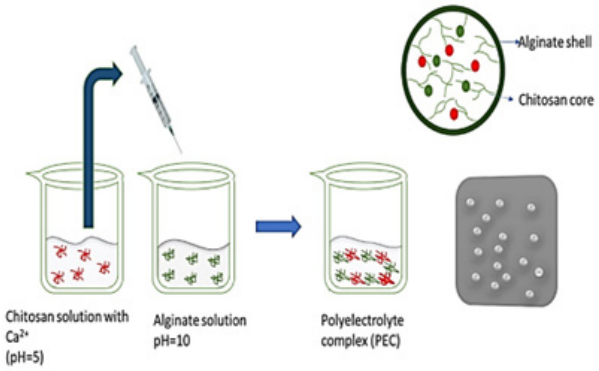

Figure 5: Alginate and chitosan interactions

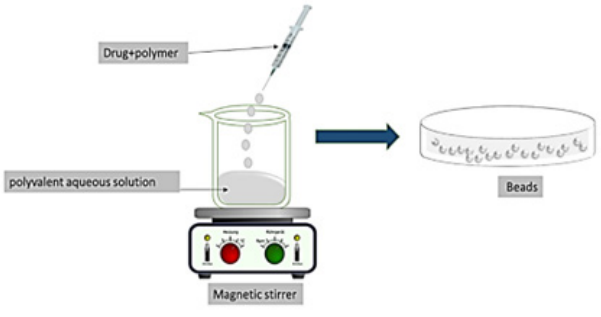

Figure 4: Hydrogel beads preparation by ionotropic gelation

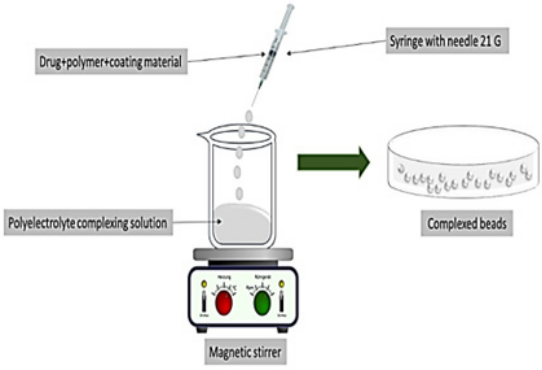

Figure 6: Hydrogel beads preparation by polyelectrolyte complexation.

solution with the protein or medication in an aqueous calcium chloride solution (Figure 3). Hydrogel beads coated with cationic polymers like chitosan and polylysine provide controlled release of protein or medicines from the hydrogel.[33-41]

Ionic Interactions Method

Ionotropic Gelation Method

Polyelectrolytes are macromolecules containing many charged groups covalently bonded to them when dissolved in a polar solvent like water. Ionotropic gelation is one of the most promising methods for preparing hydrogel beads. These beads are prepared in the presence of counterions by cross-linking the polyelectrolytes. Polymers like alginates, carboxymethyl cellulose, chitosan, gellan gum, etc., have been broadly employed for drug and cell encapsulation by this method. Natural polyelectrolytes have particular anions in their chemical composition, notwithstanding their capacity to coat the drug core and act as a controlled release system. By interacting with polyvalent cations, these anions create meshwork structures and promote gelation by attaching primarily to anion blocks. A mixture of drug and polymer solutions is prepared and then added dropwise to the aqueous solution of polyvalent cation yield in hydrogel beads, Figure 4. As cations permeate the drug-loaded polymeric droplets, they form a 3D network of ionically cross-linked polymer. As cations permeate into the polymeric droplets containing a drug, it leads to forming a 3D network of ionically cross-linked polymer. Biological molecules may be incorporated into such hydrogel beads while maintaining their three-dimensional structure under moderate conditions.[42]

To enhance the entrapment efficiency and the swelling characteristics of the drug delivery system, S. Hua *et al.* designed hydrogel beads of poly (vinyl alcohol (PVA))/sodium alginate (SA). If the SA to PVA ratio is 1:3, the beads can be a well-formed and significant improvement in entrapment efficiency.[43]

J.S. Patil *et al.* created stavudine hydrogel beads utilizing an ionotropic gelation process using polymers chitosan and alginate to extend the drug delivery system's release time. It was shown that the formulation batches containing both the polymers, *i.e.,* chitosan and alginate, released the drug for more than 12 hours whereas the batches with alginate alone released the drug for up to 10 hours.[44]

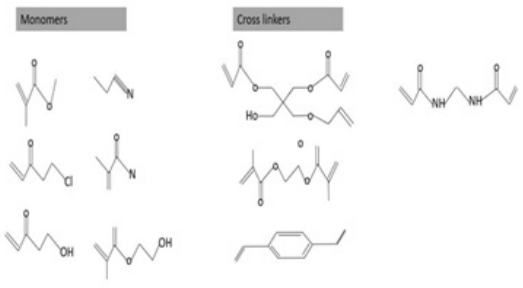

Figure 7: Chemical structure of monomers and cross-linkers

Improvement of Physical Characteristics of Hydrogel Beads

Blending polymers has proven to be a promising strategy for giving hydrogel beads desired characteristics in practical applications. A polymer blend or a new compound result from such combinations. For example, when the combination of these polymers is introduced into the chitosan hydrogel matrix, the combined characteristics of those polymers result in a specific property of chitosan. As a result, improved mechanical and chemical properties are achieved when chitosan is combined with synthetic polyvinyl chloride (PVC) and polyvinyl alcohol (PVA). The capacity of PVA to produce intra and intermolecular hydrogen bonding with the assistance of freezing-thawing cycles is the rationale for its use as a synthetic polymer. A crystallite is formed due to this hydrogen bonding, which further acts as physical cross-linking points among PVA strands, culminating in the production of hydrogels of PVA. These chitosan-PVA hydrogel beads benefit from having no harmful impact on human cells. Generally, hydrogels are composed of polysaccharides and different biopolymers because of their excellent biocompatibility, biodegradable nature, biofunctional, and bioadhesive. For example, by employing polyvalent cations as cross-linking agents, alginate beads can be quickly produced, resulting in egg-box-shaped hydrogels. The development of a polyelectrolyte complex might emerge from an ionic interaction among the alginate's carboxyl residues and the chitosan's amino groups. Core-shell-shaped alginate-chitosan hydrogel beads are standard. They are made by slowly swirling a dropwise alginate solution into a chitosan solution (Figure 5). Therefore, beads prepared using a combination of polymers possess good characteristics such as enhanced stability, structural strength, and mechanical stability compared to beads prepared using only one polymer.[45-49]

Polyelectrolyte Complexation Technique

The associative networks developed between ions with opposite charges are polyelectrolyte complexes. (*e.g.,* networks between polymer and polymer, polymer and drug, and polymer-drug-polymer). Because hydrogel beads happen from electrostatic interaction between oppositely charged polyanions/polycations, the polyelectrolyte complexation approach can increase the performance of hydrogel beads

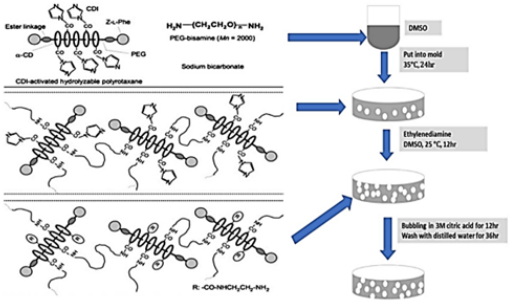

Figure 8: Preparation of cationic PEG hydrogels cross-linked by the hydrolyzable polyrotaxane.

made by the ionotropic gelation method. Mechanical stability and permeability might be improved by adding an oppositely charged additional polyelectrolyte to the hydrogel beads prepared by the ionotropic gelation method (Figure 6). Polycations, for example, generate a polyelectrolyte complex membrane on alginate beads' surface.[50,51]

Polyelectrolyte and Ionotropic Gelation Technique in Combination

To prepare hydrogel beads, Elizabeth Henao *et al.* used a combined polyelectrolyte and ionotropic gelation method. In this work, a solution of chitosan $CaCl_2$ was dissolved by continuous agitation for 2 hours and then added carboxymethyl cellulose mixture dropwise to it. Then the mixture was agitated for the next 20 minutes and maintained for 24 hours at room temperature to establish equilibrium. The mixture was then centrifuged at 3300 rpm for 30 minutes, and then from the supernatant precipitate was collected, washed thoroughly using distilled water, and then subjected to centrifugation.[42]

Stereocomplex Formation

A homopolymer is a polymer composed of repeating monomers from only one chemical source. Homopolymers such as PDLA and PLLA are semicrystalline substances composed of repeating monomers of D-lactic acid and L-lactic acid; respectively molecular weight of PLA is high and, therefore, has a melting point of 170°C in both stereoisomers. A higher melting point (230°C) is found in mixtures of PDLA and PDLA, which is due to the development of stereo completes. Ikada *et al.* explained the capacity of PLA to form stereocomplexes. Stereocomplex formation-based hydrogels have been described for use in drug delivery applications. In mixtures of triblock copolymer such as PDLA–PEG–PDLA and PLLA–PEG–PLLA, stereocomplex formation occurs. Lim *et al.* studied in detail how these triblock copolymers allow proteins like bovine serum albumin to be released from microspheres and then compared with another bovine serum albumin releasing microspheres prepared from triblock copolymer's enantiomeric form and microspheres of PLLA. The faster initial release from the microspheres of the stereo complex triblock copolymer was higher than the microspheres of PLLA, which is likely due to PEG microspheres' high water uptake ability.

In comparison to stereo complex microspheres, the release nature of Bovine serum albumin (BSA) from a pure enantiomeric homopolymer microsphere showed no significant variation. A stereo complex formulation was prepared by Lim *et al.* using enantiomeric oligo (lactic acid) whose side chains are grafted against pHEMA (poly (HEMA-g-oligolactate)). The formulation was prepared by creating a film by utilizing poly (HEMA-g-oligo (L) lactate and poly (HEMA-g-oligo (D) lactate) and dissolved in chloroform. Film cast from a solution comprising a single enantiomer of the graft copolymer was compared to degradation of the resultant film. Results showed that the 1:1 blend of the L-and D-forms degraded at a slower rate compared to a single enantiomer.[52-55]

Interactions by Hydrogen Bonding

Due to hydrogen bonding interactions, freeze-thaw cycles can be utilized to make hydrogels *in-vitro*. To create a hydrogel system, You *et al.* used a hydrogen-based bonding system that comprises strong hydrogen connections between 2-ureido-4 [H]-pyrimidinone molecules and weak hydrogen interactions between acrylic acid and N, N-dimethyl acrylamide. The unique features of monomers result from optimized radii fr and balanced interactions.[56]

A biodegradable hydrogel was developed by Yoshimura *et al.* using a straightforward technique that included esterification of succinic anhydride with starch, utilizing a catalyst 4-dimethylaminopyridine, and solvents like water or DMSO (dimethyl sulphoxide). After that, neutralization with NaOH, dialysis, and precipitation of methanol. Without the use of a cross-linker, these hydrogels were created. According to the researcher, the polymer chain aggregation leads to gelation, which is due to the reformation of hydrogen bonds at the time of dialysis.[57]

Chemical Cross-linking

Chemical cross-linking is the covalent bonding of two or more molecules, either intermolecularly or intramolecularly. In other words, chemical cross-linking is a common function of primary forces like covalent bonding. 'cross-linking reagents' or 'cross-linkers' are the reagents that are utilized for this purpose. Heat, mechanical action, and other environmental conditions are significantly more resistant to chemical cross-linking. There are many methods available for the chemical cross-linking of hydrogel beads. However, the two important methods most frequently used are condensation and free-radical polymerization. These are special methods that are usually utilized to produce degradable or non-degradable polymers. Polymers formed by these methods usually have strong cross-linking due to the presence of primary forces and thus do not cause any problems during application. On the other hand, polymers formed by the physical cross-linking method have weak cross-linking due to the absence of primary forces. Due to this reason, chemical cross-linking is more advantageous in comparison to physical cross-linking.[12,58]

Free-radical Polymerization

Chemical cross-linking is the covalent bonding of two or more molecules, either intermolecularly or intramolecularly. In other words, chemical cross-linking is a common function of primary forces like covalent bonding. 'Cross-linking reagents' or 'cross-linkers' are the reagents utilized for this purpose. Heat, mechanical action, and other environmental conditions are significantly more resistant to chemical cross-linking. There are many methods available for the chemical cross-linking of hydrogel beads. However, the two important methods most frequently used are condensation and free-radical polymerization. These are special methods usually utilized to produce degradable or non-degradable polymers. Polymers formed by these methods usually have strong cross-linking due to primary forces and thus do not cause any

problems during application. On the other hand, polymers formed by the physical cross-linking method have weak cross-linking due to the absence of primary forces. Due to this reason, chemical cross-linking is more advantageous than physical cross-linking. The monomers and cross-linkers utilized in free-radical polymerization are shown in Figure 7.[59-61]

Condensation Polymerization

When polymer chains having hydroxyl, amine, or carboxyl groups are employed, condensation processes can be used to cross-link them. They are often employed in producing polyesters and polyamides via the synthesis of polymers. To cross-link the water-soluble polymers with amide bonds, a commonly used cross-linking agent is N, N-(3-dimethylamino propyl)-N-ethyl carbodiimide (EDC). N-hydroxysuccinimide (NHS) was used in the cross-linking process to limit the possibility of side reactions and to provide the hydrogels with a higher cross-link density. Initially, this hydrogel was prepared for delivery of antimicrobial protein but later on used in Dacron prosthetic valves.

Furthermore, the previously used cross-linking agent like EDC/NHS may be employed to cross-link collagen films. This results in improved physical and mechanical properties by several orders of magnitude. Previously, researchers employed the method called ionic cross-linking to cross-linking an alginate hydrogel to enhance its physical and mechanical characteristics, but the degree of cross-linking was constrained. Mooney *et al.* later employed the EDC technique to irreversibly cross-link Poly (ethylene glycol) diamines and alginate with the quantity of PEG diamines in the hydrogel, influencing the mechanical property of the hydrogel. A polyethylene glycol network formed the connections of alpha-cyclodextrin in hydrolyzable polyrotaxane-crosslinked PEG hydrogels, which were sealed with extremely biocompatible ester groups. After that, cyclodextrin's hydroxyl groups can be activated by utilizing carbonyldiimidazole, and PEG bisamines can also be cross-linked with them. As the ester groups hydrolyze, the prepared hydrogel begins to deteriorate (Figure 8). On the other hand, the duration of hydrogel deterioration is controlled by its composition. The resulting hydrogel was employed as a substrate for soft tissue repair.[62-66]

APPLICATION

Drug Delivery to the Colon

Colon targeting drugs can help cure Crohn's disease, ulcerative colitis, and colorectal cancer using oral formulations. Proteins and peptides on oral administration are mostly unstable near the gastric region. Therefore, the colonic area is better due to less enzyme content and intensity. Polymeric carriers like chitosan are considered safe for oral administration as an absorption enhancer for poorly soluble BCS class II and class IV drugs. When combined with a carrier coat, most of the drugs whose GI degradation is high are shown to have lesser GI enzyme degradation patterns. The absorption mechanism and requirements of the colon help produce an effective formulation because chitosan is easily degradable in the colon due to the presence of specific bacterial flora. The effects of chitosan beads for insulin absorption directly relate to the amount of plasma glucose content and its relative pharmacological availability. This is due to tripolyphosphate and chitosan's presence, which provides a robust bonding and therefore improves intestinal insulin absorbability.[67]

Nasal Delivery

Nasal delivery is one of the fastest and quickest routes to deliver drugs while reaching a more significant therapeutic onset with lesser enzymatic barriers. The intranasal delivery helps deliver drugs directly reach the systemic circulation. The nasal delivery, along with permeation enhancers, produces improved absorption. The mucoadhesive nasal formulations are effective due to their prolonged adhesive contact and lesser dose depletion. The mucoadhesion requires a polymer network free of moisture and provides closer contact that helps influence a decrease in the rate of ciliary clearance rate of mucus and improves drug absorption. Polymer-like chitosan with higher cationic charge density is a polysaccharide that prolongs the time of drug retention. Due to its positive charge, the interaction of charge with the mucous layer or utilizing the negative charge of mucosal sialic acid residues produces improved absorption, *i.e.,* by unlocking tight junctions by paracellular route in the epithelial cells. The use of polymeric beads for therapy helps adjust the release patterns of drugs and adjust specific treatment criteria. Chitosan has been utilized in many formulations as an anticancer agent, proteins, vaccines, antibiotics, antihypertensives, etc. Chitosan polymer and mucus glycoprotein chains have shown better penetration patterns and improved water absorption in chitosan-based microsphere formulations.[68]

Gastroenteric Delivery

Hydrogel beads are multi-unit oral formulations whose release patterns can be controlled better than single-unit dosage forms. NSAIDS like Ketoprofen are profoundly used in muscle and joint pain treatment. These drugs have a lesser half-life and faster GI absorption patterns. Therefore, using hydrogel beads directs to control the varying transit speeds and the impulse of stomach emptying, creating a reliable formulation. Problems associated with GI irritation and ulceration are highly reduced due to the protective barrier formation of polymer over the surface of the drug. Using multi-unit doses helps improve absorption patterns, preventing elevated drug release and concentration throughout the body.[69]

Ocular Delivery

Occular delivery is one of the most challenging ways to deliver medications due to its anatomical and physiological barriers with limited drug grasp towards the targeted sites. The factors like tear fluid insurgency, residence duration, restricted permeation, and absorption rate throughout the corneal region. Due to these problems, there is a problem related to poor therapeutic action, and regular administration of drugs is required. One of the methods that can improve residence period and diffusion in the cornea can be by use of ocular bioadhesives, which directs to improved drug absorption

and bioavailability. Polymers involved in hydrogel beads are effective in improving mucoadhesive properties and residence periods. Some researchers have used dexamethasone sodium phosphate and chloramphenicol with gellan gum as a polymer base to create an in-situ ophthalmic gel. As the concentration of gellan gum is higher, the drug release is decreased. The use of curcumin-loaded micelles provides an improved ocular retention period and corneal permeability to the in-situ gel formulations.[70]

Polymers Used in Hydrogel Beads Preparation

The polymers and their unique characteristics, flexible and adaptable nature acquired a great place in the drug formulation process. The polymers have exceptional properties like preserving drug release rates with lower molecular weight. Polymers also provide improved blood circulation and better targeting behavior due to their improved retention behavior. Polymers help support sustained drug delivery profiles producing higher therapeutic action and pharmacological benefits. Their property to adjust release rates makes them versatile to include in various formulations like solids, liquids, or even semi-solid formulations. Recently, many newer formulations in the limelight like controlled, modified, and sustained-release formulations containing pharmaceutical and biopharmaceutical agents require these polymers as excipients.[71]

Chitosan

The chitosan is a the deacetylated derivative of chitin dates back almost 150 years from now as it was considered a useful biodegradable outmost ubiquitous naturally available biopolymer. This polymer has shown better binding properties with certain compounds alongside certain organic and heavy metal species. Chitin, being a (1,4)-N-acetyl-D-glucosamine-based homopolymer species, was usually found in shrimps, a few fungal species, and in the exoskeletons of insects. The basic units involved in chitosan were N-acetylglucosamine and D-glucosamine, produced in a basic medium from fractional deacetylation of parent compound chitin.

The presence of N-deacetylation causes the pKa value to range near 6.5 making chitosan water-insoluble. Some of the broad application of chitosan includes tissue engineering, as a non-parenteral formulation excipient, and in some aspects of biomedical research. The chitosan is better known for its adaptability, biocompatibility, and lesser toxicity traits making it an ideal candidate for most oral formulations for its sustained, controlled, or modified release patterns. The other benefits are seen in their pH-reliant release patterns in GIT. The series of polymers like sodium alginate (SA), polycaprolactone (PCL), gelatin (G), and polyethylene glycol (PEG) have been practical to generate complexes that can help induce micro or nanoparticle inside the hydrogel formulations with stable and efficient results.[72]

Alginate

The properties of alginates involve both thickening and gelling abilities. The most used derivative of alginate is sodium alginate which is used in producing hydrogel beads in the presence of cationic species like calcium etc., and requires a basic or low pH environment. The innate qualities of polymeric alginate hydrogels involve high water availability, mucoadhesive, biocompatible, low production cost, and ease in production. These characteristics make alginates suitable for use in many biomedical processes. Some of the modified alginate species are also found helpful in controlled release and targeted release formulations manufacture; some of the modified alginate species include hydrophobically modified alginate, alginate-PEI based chitosan long-chain aliphatic modifiers. The graft species of alginate-PEI alongside alginate polysaccharide chains were produced based on Schiff-base reaction, which led to the formation of alginate-g-PEI. This alginate-g-PEI species had beneficial modifiable characteristics but tended to show little cytotoxic effects.[73]

Carrageenan

These are the natural-based linear chain sulfate-based polysaccharides originating from edible red seaweed species. Carrageenans/carrageenins have many properties ranging from gelling, emulsifying, stabilizing, and thickening capabilities compared to naturally available agar. The cost of carrageenan is economical, and their hydrophilic characteristics tend to impersonate glycosaminoglycans (GAGs) to an extent; hence used are most commercially used. The three commercially available species of carrageenan include:

- ***Kappa (K):*** This contains one negative ion, consisting of solid disaccharide characteristics, making it a rigid gel structured compound. The kappa varied is derived from *sappaphycus cottonii* species. The κ-carrageenan have fewer aggregation properties than other carrageenans due to 2- sulfate groups in their helical structures.
- ***T-type:*** This variant has a reasonable amount of sulfate, and soft gels can be produced using freeze-thaw techniques. These variants are derived from *Eucheuma cottonii*.
- ***λ-type:*** These contain a high quantity of sulfate and are likely capable of producing limited gel properties, but the use of proteins can lead to better gel formation instead of using water during formulation.

It is important to note that ions concentration in carrageenans establishes the gelling and melting characters as the electrolytes have the capability to create/stabilize the gel nature of the compound. The thermosensitivity of hydrogels is due to the hydrophilicity of polysaccharides along with $Ca^{2}+$ and K^{+} ions or without any salts involved. At the high temperature, carrageenans melt and gelation is activated in the biopolymer, this enables the development of different kinds of gels and their adaptive nature.[74]

Guar Gum

Guar gum/guaran is a polysaccharide of galactomannan, *i.e.,* derived from the Cyamopsis tetragonolobus plant. This polysaccharide is capable of stabilizing and thickening food and other industrial-grade products. The guar gum is water-soluble and is made of (1→4)-ß-D-mannopyranosyl linked onto (1→6) connection making it a non-ionic polymer. The extensive use of guar gum is due to its economic cost, easy availability, and immense potential for most health care, cosmetic and medicinal products. The manufacture and

formulation of most matrix, microsphere-based controlled dosage forms involve using guar gum as a carrier system. Also, the protective barrier activity to avoid microbial corrosion near the intestinal region make it suitable for colon-specific delivery excipient formulation choice. The modification of guar gum is easy due to the presence of the OH group, therefore making it incorporate many functional moieties for better drug release control. Some examples of these comprise carboxymethyl-based phosphate and polyacrylamide groups to induce superior formulation capabilities. Cross-linking with cationic moieties like Ba^{2+} and grafted gum-poly (ε-caprolactone) can induce many biological capabilities in the formulations.[75]

Gellan Gum

Gellan gum is a hydrophilic linear exopolysaccharide anionically obtained from Sphingomonas paucimobilis fermentation processes. They are 1 to 2×10^6 Da in-mol. Weight and have high acyl groups in them. The primary contents involved in gellan gum are 60% glucose alongside 20% rhamnose and 20% glucuronic acid, which also make up the structural backbone of gellan gum. The thermostability and higher lucidity are due to its gelling qualities making it more toxicity free, less biodegradable, and highly compatible during formulations. As a food base and medicinal base, gellan gum can also produce robust gels with lesser concentrations. Along with their mucoadhesive capabilities, their overall characteristics make them suitable to use in controlled release systems and produce hydrogel beads alongside cationic moieties presence like Ca^{2+}.[76]

Carbopol

This is an acrylic-based polymer used as a pH-stimuli sensitive carrier with most pharma- and cosmeceutical application. The carbopol is used as an excipient base in most hydrogels as their gelling, and swelling properties make them suitable to formulate as a controlled/targeted release dosage system. They are also occasionally employed as a thickening, emulsifying, and suspending agents. One of the carpool compounds, namely carbopol® 974P, is used in oral formulation due to their polymerization with acrylic acid-base. This shows the high microbiological resistance and thickening capabilities of carbopol making it suitable to formulate as a hydrogel bead to obtain a controlled release product. Their stimuli-responsive nature is also considered applicable w.r.t pH, temperature, etc. The most seen property of carbopol is the distribution effects of ingredients when in contact with an alkaline medium causing high swelling characteristics near the alkaline pH range.[77-79]

Recent Studies on Hydrogel Beads

Study-1

Mehdi Yadollahi *et al.* created a hybrid system of antibacterial chitosan/silver bio-nano hydrogel beads using a one-pot synthesis method. The preparation was done using physical cross-linking using cross-linker tripolyphosphate, on the other hand utilizing a nanoparticle-based of silver base. The X-ray diffraction and scanning electron microscopy test were performed to determine antibacterial and swelling properties. The nanocomposite hydrogels showed effective antimicrobial action against bacterial species of *Escherichia coli* and *Staphylococcus aureus* Swelling capabilities were improved due to AgNPs formation. Controlled delivery property, efficacy, and *in-vitro* drug release test showed prolonged and controlled release patterns and high AgNPs content were achieved. Thus the results concluded that the use of this medication for controlled delivery could be considered as it has produced effective results.[80]

Study-2

TK. Giri *et al.* formulated pH-responsive hydrogel beads by utilizing a capsaicin entrapped nanoliposome. To obtain maximum colon distribution of drugs, the formulation was encapsulated along alginate-based hydrogels to form beads coated using eudragit S-100. Liposomes were created using soya lectin and cholesterol, whereas hydrogel beads were created using an ionotropic gelation procedure with a eudragit coat. Liposomes were examined for entrapment efficiency, size, *in-vitro* drug release, etc. The release studies demonstrated that the colonic drug reach was almost 65% compared to a lesser reach with ordinary hydrogel beads. The drug release showed improvement for 5 hours, and about 99.3% release was observed until 24 hours. Thus this study proved the efficiency of hydrogel beads to reach improved colon reach alongside better release characteristics compared to normal formulations.[81]

Study-3

Hui-Peng Lim *et al.* worked on formulating pH-responsive composite hydrogel beads of alginate/κ- carrageenan made of an oral insulin-based controlled delivery system. As the subcutaneous delivery of insulin shows partial compliance from the patient's views, the creation of encapsulated insulin formulations has helped create a hostile stomach acid insensitive formulation and intestinally controlled release formulation. The extrusion-dripping technique is introduced to create hydrogel beads based on naturally obtained biopolymers such as alginate and -carrageenan. The primary delivery was observed in gastric fluids, where 65% of insulin was biologically active in gastric fluids. These results prove the potential of incorporating insulin as a hydrogel formulation as a potential delivery route.[82]

Study-4

Ping Sun *et al.* formulated glipizide pH-sensitive hydrogel beads using chitosan-triphosphate using the ionotropic gelation method. The process involved use of chitosan (CS)-tripolyphosphate (TPP) to achieve controlled release beads. FT-IR and scanning electron microscopy were used to define the structural and morphological characteristics of the beads. Swelling characteristics and behavior of beads were studied by factors like concentration and volume ratios of drug and excipients used, the drug to polymer ratio, and time to achieve cross-linking. The swelling ratio was found to increase w.r.t the decrease in pH, *i.e.,* at pH 1.5; the swelling was high, and

at pH 6.8: it was comparatively slow. The results showed a maximum drug release of 90% in the pH 1.5 region and a lower drug release of 35% near the pH 6.8 region. These values stated that the incorporation of a ph-sensitive controlled release device showed promising results for the oral administration of glipizide-loaded hydrogel beads.[83]

Study-5

R.V. Kulkarni *et al.* formulated a pH-responsive intestinal targeted system for ketoprofen delivery. This system uses an interpenetrating network (IPN) which involves the use of sodium alginate (SA) alongside polyacrylamide grafted j-carrageenan (PAAm-g-CG). PAAm-g-CG was prepared by a free radical polymerization reaction and hydrolyzed using alkali in the presence of nitrogen gas. The amorphous states of beads were studied by X-ray diffraction and SEM for particle shape. The swelling studies proved the pH-responsiveness of the beads, in which the results showed almost 10% drug release at 1.2 pH whereas up to 90% drug release from a 7.4 pH medium. This proved lesser stomach ulceration and irritation near the gastric region when studied on albino rats. Thus the promising results can be extrapolated to state that the use of IPN-based pH-sensitive ketoprofen beads has beneficial effects in the targeting intestine.[84]

Study-6

Torelli-Souza *et al.* formulated an AL-CS (alginate-chitosan) hydrogel beads of an β-lapachone drug as controlled delivery system for colon cancer and studied for physicochemical and swelling behaviors. The results showed a diameter range of 1mm with lesser permeability and improved stability. The kinetic profiles were decent with minimal burst activities when studied for in vitro drug release in an acidic environment for 72 hours study. The beads proved their resistance to acidic contents. Thus, the controlled release nature of hydrogel beads provided an effective colorectal therapy with lesser side effects.[85]

Future Perspectives

Hydrogel systems are extensively explored in numerous fields. Still, unlike other drug delivery means, its full potential is yet to be analyzed as a delivery system. The hydrogels have a future place in tissue scaffolds, and can be presented as magnetic nanocomposite hydrogel beads for the site-specific delivery of anticancer drugs in the colon and other similar tissues. These agents can be extended in encapsulating lipid natured agents, which are prone to be oxidized, such as phospholipids. They have a scope in carrying antimicrobials, flavors, vitamins, and antioxidants. A wide range of applications is foreseen in food-grade colloidal delivery systems that can enhance their water dispersibility, bioavailability, and chemical stability. Hydrogel beads can be presented as drug delivery device by tagging with biosensors such as enzymes, antibodies, living cells, or tissues as a diagnostic.[86,87]

CONCLUSION

Hydrogels uses a variety of natural or synthetic polymers with unique structures and swelling capabilities that allow them to contain large volumes of water. The capacity to respond to external stimuli like as pH, temperature, and ions may have paved the way for medication delivery. They are a strong contender for environmental and biological applications as implants or materials for the removal of harmful pollutants due to their biocompatibility, biodegradability, and versatility in preparation. Tissue engineering, contact lenses, hygiene products, drug delivery, and other applications use hydrogel systems. While biomedical applications are presently limited to the laboratory, a lot of research can be done in this area to help improve commercialization.

ACKNOWLEDGMENT

The authors are highly thankful to the Krupanidhi college of pharmacy for providing essential facilities and guidance to accomplish this review study.

REFERENCES

1. Prajapati VD, Jani GK, Khutliwala TA, *et al.* Raft forming system - An upcoming approach of gastroretentive drug delivery system. J Control Release 2013; 168: 151–165.
2. Jassal M, Nautiyal U, Kundlas J, *et al.* A review: Gastroretentive drug delivery system (grdds). Indian J Pharm Biol Res 2015; 3: 82–92.
3. Mandal UK, Chatterjee B, Senjoti FG. Gastro-retentive drug delivery systems and their in vivo success: A recent update. Asian J Pharm Sci 2016; 11: 575–584.
4. Iglesias N, Galbis E, Valencia C, *et al.* Biodegradable double cross-linked chitosan hydrogels for drug delivery: Impact of chemistry on rheological and pharmacological performance. Int J Biol Macromol 2020; 165: 2205–2218.
5. Dreiss CA. Hydrogel design strategies for drug delivery. Curr Opin Colloid Interface Sci 2020; 48: 1–17.
6. Shariatinia Z, Jalali AM. Chitosan-based hydrogels: Preparation, properties and applications. Int J Biol Macromol 2018; 115: 194–220.
7. Wang K, Hao Y, Wang Y, *et al.* Functional Hydrogels and Their Application in Drug Delivery, Biosensors, and Tissue Engineering. Int J Polym Sci 2019; 2019: 1–14.
8. Amiri M, Khazaeli P, Salehabadi A, *et al.* Hydrogel beads-based nanocomposites in novel drug delivery platforms: Recent trends and developments. Adv Colloid Interface Sci 2021; 288: 1–40.
9. Hoffman AS. Hydrogels for biomedical applications. Adv Drug Deliv Rev 2012; 64: 18–23.
10. Gyles DA, Castro LD, Silva JOC, *et al.* A review of the designs and prominent biomedical advances of natural and synthetic hydrogel formulations. Eur Polym J 2017; 88: 373–392.
11. Datta N, Pal M, Roy U, *et al.* A review on hydrogel as drug delivery system. World J Pharm Res 2014; 13: 578–599.
12. Ullah F, Othman MBH, Javed F, *et al.* Classification, processing and application of hydrogels: A review. Mater Sci Eng C 2015; 57: 414–433.
13. Silva AKA, Richard C, Bessodes M, *et al.* Growth factor delivery approaches in hydrogels. Biomacromolecules 2009; 10: 9–18.
14. Ahmad S, Ahmad M, Manzoor K, *et al.* International Journal of Biological Macromolecules A review on latest innovations in natural gums based hydrogels : Preparations & applications. Int J Biol Macromol 2019; 136: 870–890.

15. Gulrez S, Al-assaf S, Phillips GO. Hydrogels : Methods of Preparation , Characterisation and Applications. 2011; 117–150.
16. Ahmed EM. Hydrogel : Preparation , characterization , and applications : A review. J Adv Res 2015; 6: 105–121.
17. Narayanaswamy R, Torchilin VP. Hydrogels and Their Applications in Targeted Drug Delivery. 2019; 24: 603.
18. Wang Y, Wang J, Yuan Z, *et al.* Chitosan cross-linked poly(acrylic acid) hydrogels: Drug release control and mechanism. Colloids Surfaces B Biointerfaces 2017; 152: 252–259.
19. Hoshino Y, Arata Y, Yonamine Y, *et al.* preparation of nanogel-immobilized porous gel beads for affinity separation of proteins: Fusion of nano and micro gel materials. Polym J 2015; 47: 220–225.
20. Basri M, Wan Yunus WMZ, Yoong WS, *et al.* Immobilization of lipase from Candida rugosa on synthetic polymer beads for use in the synthesis of fatty esters. J Chem Technol Biotechnol 1996; 66: 169–173.
21. Fleischmann C, Lievenbrück M, Ritter H. Polymers and dyes: Developments and applications. Polymers (Basel) 2015; 7: 717–746.
22. Nandini Sahu, Diksha Gupta, Ujjwal Nautiyal. Hydrogel: Preparation, Characterization and Applications. Asian Pacific J Nurs Heal Sci 2020; 3: 1–11.
23. Niu H, Wang F, Weiss RA. Hydrophobic/hydrophilic triblock copolymers: Synthesis and properties of physically cross-linked hydrogels. Macromolecules 2015; 48: 645–654.
24. Li L, Cheng J, Wen X, *et al.* Synthesis and characterization of suspension polymerized styrene-divinylbenzene porous microsphere using as slow-release-active carrier. Chinese J Chem Eng 2006; 14: 471–477.
25. Hoare TR, Kohane DS. Hydrogels in drug delivery: Progress and challenges. Polymer (Guildf) 2008; 49: 1993–2007.
26. Javakhishvili I, Hvilsted S. Miktoarm core-crosslinked star copolymers with biologically active moieties on peripheries. Polym Chem 2010; 1: 1650–1661.
27. Wang H, Heilshorn SC. Adaptable Hydrogel Networks with Reversible Linkages for Tissue Engineering. Adv Mater 2015; 27: 3717–3736.
28. Yan X, Zheng B, Huang F. Integrated motion of molecular machines in supramolecular polymeric scaffolds. Polym Chem 2013; 4: 2395–2399.
29. De Jong SJ, Van Eerdenbrugh B, Van Nostrum CF, *et al.* Physically cross-linked dextran hydrogels by stereocomplex formation of lactic acid oligomers: Degradation and protein release behavior. J Control Release 2001; 71: 261–275.
30. Ito M, Tateishi T, Taguchi T. Synthesis and evaluation of PEG derivatives for cross-linking cells. Macromol Symp 2007; 249–250: 159–161.
31. Maitra J, Shukla VK. Cross-linking in Hydrogels - A Review. Am J Polym Sci 2014; 4: 25–31.
32. Kenawy ER, Kamoun EA, Mohy Eldin MS, *et al.* Physically cross-linked poly(vinyl alcohol)-hydroxyethyl starch blend hydrogel membranes: Synthesis and characterization for biomedical applications. Arab J Chem 2014; 7: 372–380.
33. Lee KY, Mooney DJ. Alginate: Properties and biomedical applications. Prog Polym Sci 2012; 37: 106–126.
34. Ertesvåg H. Alginate-modifying enzymes: Biological roles and biotechnological uses. Front Microbiol 2015; 6: 1–10.
35. Utech S, Prodanovic R, Mao AS, *et al.* Microfluidic Generation of Monodisperse, Structurally Homogeneous Alginate Microgels for Cell Encapsulation and 3D Cell Culture. Adv Healthc Mater 2015; 4: 1628–1633.
36. Zhang Z, Zhang R, Zou L, *et al.* Protein encapsulation in alginate hydrogel beads: Effect of pH on microgel stability, protein retention and protein release. Food Hydrocoll 2016; 58: 308–315.
37. Dim N. Synthesis and characterization of silver nanoparticles and its immobilization on alginate coated sutures for the prevention of surgical wound infections and the in vitro release studies. Int J Nano Dimens 2012; 2: 205–212.
38. Ren Y, Xie H, Liu X, *et al.* Comparative investigation of the binding characteristics of poly-L-lysine and chitosan on alginate hydrogel. Int J Biol Macromol 2016; 84: 135–141.
39. Chen H, Xing X, Tan H, *et al.* Covalently antibacterial alginate-chitosan hydrogel dressing integrated gelatin microspheres containing tetracycline hydrochloride for wound healing. Mater Sci Eng C 2017; 70: 287–295.
40. Augustine R, Ashkenazi DL, Arzi RS, *et al.* Nanoparticle-in-microparticle oral drug delivery system of a clinically relevant darunavir/ritonavir antiretroviral combination. Acta Biomater 2018; 74: 344–359.
41. Costa MJ, Marques AM, Pastrana LM, *et al.* Physicochemical properties of alginate-based films: Effect of ionic cross-linking and mannuronic and guluronic acid ratio. Food Hydrocoll 2018; 81: 442–448.
42. Henao E, Delgado E, Contreras H, *et al.* Polyelectrolyte Complexation versus Ionotropic Gelation for Chitosan-Based Hydrogels with Carboxymethylcellulose, Carboxymethyl Starch, and Alginic Acid. Int J Chem Eng 2018; 2018: 1–12.
43. Hua S, Ma H, Li X, *et al.* pH-sensitive sodium alginate/poly(vinyl alcohol) hydrogel beads prepared by combined Ca2+ cross-linking and freeze-thawing cycles for controlled release of diclofenac sodium. Int J Biol Macromol 2010; 46: 517–523.
44. Patil JS, Kamalapur M V., Marapur SC, *et al.* Lonotropically gelled chitosan-alginate complex hydrogel beads: Preparation, characterization and In-vitro evaluation. Indian J Pharm Educ Res 2012; 46: 248–252.
45. Luo Y, Wang Q. International Journal of Biological Macromolecules Recent development of chitosan-based polyelectrolyte complexes with natural polysaccharides for drug delivery. Int J Biol Macromol 2014; 64: 353–367.
46. Gierszewska M, Ostrowska-czubenko J, Chrzanowska E. pH-responsive chitosan/alginate polyelectrolyte complex membranes reinforced by tripolyphosphate. Eur Polym J 2018; 101: 282–290.
47. Mahdavinia GR, Soleymani M, Etemadi H, *et al.* Model protein BSA adsorption onto novel magnetic chitosan/PVA/laponite RD hydrogel nanocomposite beads. Int J Biol Macromol 2017; 107: 719–729.
48. Mahdavinia GR, Soleymani M, Sabzi M, *et al.* Novel magnetic polyvinyl alcohol/laponite RD nanocomposite hydrogels for efficient removal of methylene blue. J Environ Chem Eng 2017; 5: 2617–2630.
49. Gutha Y, Pathak JL, Zhang W, *et al.* Antibacterial and wound healing properties of chitosan/poly(vinyl alcohol)/zinc oxide beads (CS/PVA/ZnO). Int J Biol Macromol 2017; 103: 234–241.
50. Patil P, Chavanke D, Wagh M. A review on ionotropic gelation method: Novel approach for controlled gastroretentive gelispheres. Int J Pharm Pharm Sci 2012; 4: 27–32.

51. Srinivas L, Ramana Murthy K V. Preparation and evaluation of polyelectrolyte complexes for oral controlled drug delivery. Asian J Pharm 2010; 4: 69–78.
52. Jong SJ De, Bosch JJK Den, Schuyl PJW, *et al.* Monodisperse Enantiomeric Lactic Acid Oligomers : Preparation , Characterization , and Stereocomplex Formation. 1998; 31: 1–6.
53. Lim DW, Choi SH, Park TG. A new class of biodegradable hydrogels stereocomplexed by enantiomeric oligo (lactide) side chains of poly (HEMA- g -OLA) s. 2000; 471: 464–471.
54. Lim DWOO, Park TAEG. Stereocomplex Formation between Enantiomeric PLA – PEG – PLA Triblock Copolymers : Characterization and Use as Protein-Delivery Microparticulate Carriers. 2000; 1615–1623.
55. Metathesis O, Metath- O. Stereocomplex Formation between Enantiomeric. 1987; 1: 904–906.
56. Y, Yang J, Zheng Q, *et al.* Ultra - stretchable hydrogels with hierarchical hydrogen bonds. Sci Rep 2020; 10: 1–8.
57. Yoshimura T, Yoshimura R, Seki C, *et al.* Synthesis and characterization of biodegradable hydrogels based on starch and succinic anhydride. 2006; 64: 345–349.
58. De Santa Maria LC, Aguiar MRMP, Guimarães PIC, *et al.* Synthesis of cross-linked resin based on methacrylamide, styrene and divinylbenzene obtained from polymerization in aqueous suspension. Eur Polym J 2003; 39: 291–296.
59. Hennink WE, van Nostrum CF. Novel cross-linking methods to design hydrogels. Adv Drug Deliv Rev 2012; 64: 223–236.
60. Reviews P. Crosslinking Of Polysaccharides : Methods And Applications Crosslinking Of Polysaccharides : Methods And Applications. 2016; 6: 1–11.
61. Edman P, Ekman B, Sjöholm I. Immobilization of proteins in microspheres of biodegradable polyacryldextran. J Pharm Sci 1980; 69: 838–842.
62. Kuijpers AJ, Wachem PB Van, Luyn MJA Van, *et al.* In vivo and in vitro release of lysozyme from cross-linked gelatin hydrogels : a model system for the delivery of antibacterial proteins from prosthetic heart valves. 2000; 67: 323–336.
63. Ohan MP, Weadock KS, Dunn MG. Synergistic effects of glucose and ultraviolet irradiation on the physical properties of collagen. 2001; 60: 384–391.
64. Kuijpers AJ, Engbers GHM, Meyvis TKL, *et al.* Combined Gelatin - Chondroitin Sulfate Hydrogels for Controlled Release of Cationic Antibacterial Proteins. 2000; 33: 3705–3713.
65. P, Lee KY, Mooney DJ. Rigidity of Two-Component Hydrogels Prepared from Alginate and Poly (ethylene glycol) - Diamines. 1999; 32: 5561–5566.
66. Ichi T, Watanabe J, Ooya T, *et al.* Controllable Erosion Time and Profile in Poly (ethylene glycol) Hydrogels by Supramolecular Structure of Hydrolyzable Polyrotaxane. 2001; 2: 204–210.
67. Jain SK, Jain A, Gupta Y, *et al.* Design and development of hydrogel beads for targeted drug delivery to the colon. AAPS PharmSciTech 2007; 8: 1–8.
68. Abdel Mouez M, Zaki NM, Mansour S, *et al.* Bioavailability enhancement of verapamil HCl via intranasal chitosan microspheres. Eur J Pharm Sci 2014; 51: 59–66.
69. Kulkarni R, Sa B. Enteric delivery of ketoprofen through functionally modified poly(acrylamide-grafted-xanthan)-based pH-sensitive hydrogel beads: Preparation, in vitro and in vivo evaluation. J Drug Target 2008; 16: 167–177.
70. Das M, Giri TK. Hydrogels based on gellan gum in cell delivery and drug delivery. J Drug Deliv Sci Technol 2020; 56: 101586.
71. Rao GU. International Journal of Comprehensive Pharmacy Buoyant Sustained Release Drug Delivery Systems Current Potentials Advancements and Role of Polymers : a Review. 2012; 03: 1–5.
72. Kumar A, Vimal A, Kumar A. Why Chitosan? From properties to perspective of mucosal drug delivery. Int J Biol Macromol 2016; 91: 615–622.
73. Mohy Eldin MS, Kamoun EA, Sofan MA, *et al.* L-Arginine grafted alginate hydrogel beads: A novel pH-sensitive system for specific protein delivery. Arab J Chem 2015; 8: 355–365.
74. Popa EG, Gomes ME, Reis RL. Cell delivery systems using alginate-carrageenan hydrogel beads and fibers for regenerative medicine applications. Biomacromolecules 2011; 12: 3952–3961.
75. Yang H, Wang W, Zhang J, *et al.* Preparation, characterization, and drug-release behaviors of a pH-sensitive composite hydrogel bead based on guar gum, attapulgite, and sodium alginate. Int J Polym Mater Polym Biomater 2013; 62: 369–376.
76. Dave PN, Gor A. Natural polysaccharide-based hydrogels and nanomaterials: Recent trends and their applications. Elsevier Inc. Epub ahead of print 2018. DOI: 10.1016/B978-0-12-813351-4.00003-1.
77. Paker-Leggs S, Neau SH. Propranolol forms affect properties of Carbopol-containing extruded-spheronized beads. Int J Pharm 2008; 361: 169–176.
78. López-Cacho JM, González-R PL, Talero B, *et al.* Robust optimization of alginate-Carbopol 940 bead formulations. Sci World J 2012; 2012: 1–15.
79. Neau SH, Chow MY, Hileman GA, *et al.* Formulation and process considerations for beads containing Carbopol® 974P, NF resin made by extrusion-spheronization. Int J Pharm 2000; 199: 129–140.
80. M, Farhoudian S, Namazi H. One-pot synthesis of antibacterial chitosan/silver bio-nanocomposite hydrogel beads as drug delivery systems. Int J Biol Macromol 2015; 79: 37–43.
81. Giri TK, Bhowmick S, Maity S. Entrapment of capsaicin loaded nanoliposome in pH responsive hydrogel beads for colonic delivery. J Drug Deliv Sci Technol 2017; 39: 417–422.
82. Lim HP, Ooi CW, Tey BT, *et al.* Controlled delivery of oral insulin aspart using pH-responsive alginate/κ-carrageenan composite hydrogel beads. React Funct Polym 2017; 120: 20–29.
83. Sun P, Li P, Li YM, *et al.* A pH-sensitive chitosan-tripolyphosphate hydrogel beads for controlled glipizide delivery. J Biomed Mater Res - Part B Appl Biomater 2011; 97 B: 175–183.
84. Kulkarni R V., Boppana R, Krishna Mohan G, *et al.* PH-responsive interpenetrating network hydrogel beads of poly(acrylamide)-g-carrageenan and sodium alginate for intestinal targeted drug delivery: Synthesis, in vitro and in vivo evaluation. J Colloid Interface Sci 2012; 367: 509–517.
85. Yang Z, Peng H, Wang W, *et al.* Crystallization behavior of poly(ε-caprolactone)/layered double hydroxide nanocomposites. J Appl Polym Sci 2010; 116: 2658–2667.
86. Mohammadi R, Saboury A, Javanbakht S, *et al.* Carboxymethylcellulose/polyacrylic acid/starch-modified Fe3O4 interpenetrating magnetic nanocomposite hydrogel beads as pH-sensitive carrier for oral anticancer drug delivery system. Eur Polym J 2021; 153: 110500.
87. Huang J, Wang Q, Chu L, *et al.* Liposome-chitosan hydrogel bead delivery system for the encapsulation of linseed oil and quercetin: Preparation and in vitro characterization studies. Lwt 2020; 117: 108615.