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A literature review on preparation, characterization, and application of hydrogel

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Abstract
The study aimed to assess the widespread usage of hydrogels in pharmaceutical formulations. Hydrogels are hydrophilic polymer matrices that can hold an enormous volume of water and swell in water, making them non-toxic and ideal for drug delivery systems. The clinical applications of hydrogels have shown that they provide therapeutic benefits. Hydrogels are durable, easily self-healable, and can shield the surface of accurate components from damage. Hydrogels can be physically cross-linked through various techniques, including heating/cooling a polymer solution, ionic interaction, complex coacervation, H-bonding, and freeze-thawing. Hydrogels play a critical role in pharmaceutical technology as a drug delivery system.

Keywords: Hydrogels, complex coacervation, H-bonding, freeze-thawing, drug delivery system

1. Introduction

Principle

In 1960, Wichterle and Lím discovered hydrogels, a remarkable material that creates a three-D network of hydrophilic polymers. This network can soak up a significant amount of aqua and maintain its structural integrity through physical or chemical cross-linking of individual polymer chains. Any material that contains no less than 10% of water in its total capacity is classified as a hydrogel. Due to their high-water content, hydrogels possess a level of flexibility synonymous with inherent tissue, making them useful for all-around medical implementation. Hydrogels owe their hydrophilicity to the existence of hydrophilic groups like -NH_2, -COOH, -OH, -$CONH_2$, -CONH-, and -SO_3H, which enable the hydrogel to absorb water and maintain its structure [46].

Application of Hydrogel

Synthetic biomaterials are known as hydro with various purposes in the medical and pharmaceutical industries. Their physicochemical properties are exceptional, making them flexible and compatible with biological systems. Hydrogels contain a high percentage of water and are consistently soft, closely mimicking natural living tissue, making them the most biocompatible synthetic biomaterials available. This characteristic is what makes them biocompatible.

Hydrogels can be customized to react to varying surroundings, such as pH, temperature, and enzymatic activities at sites affected by diseases. As a result, they are considered "smart" or "intelligent" hydrogels that function as drug delivery systems based on depots for treating a wide range of illnesses. Sol-gel transformation can be effectively triggered by pH, one of the most frequently used stimuli. Heat sensitivity is another characteristic that can be exhibited by hydrogels. Most temperature-sensitive hydrogels remain in a sol state at room temperature and solidify to form a gel at increased temperature, typically the heat of the physique. Hydrogels have stable biocompatibility, which makes them suitable for use as contact lenses and as a barrier in the peritoneum. In cancer treatment, hydrogels have been found to be a secure and efficient drug delivery system that utilizes depot-based technology, thanks to their unique chemical and physical properties. However, the use of hydrogels for carrying hydrophobic drugs has been limited in the past due to the restricted amount and consistency of hydrophobic medications that can be loaded into hydrogel matrices.

In order to enhance the ability of hydrogels to load drugs, they have been restricted to networks consisting of tiny micelles that have an average particle size of equal to or less than 200 nanometers. This method has proven to be effective in increasing the drug-loading capacity of hydrogels. The hydrogels' micellar structure, consisting of a hydrophilic shell and hydrophobic core, allows for the encapsulation of both hydrophilic and hydrophobic compounds, making it possible to deliver multiple drugs in a single dose locally. Hydrogel-based delivery systems that can provide hydrophobic drugs are essential for local chemotherapy, as a significant number of chemotherapeutic drugs have low water solubility and are unable to achieve Preclinical studies and clinical trials have shown that injectable solutions, with adequate concentrations, can demonstrate therapeutic efficacy. Integrating low-soluble drugs into hydrogels can increase drugs' aqueous solubility and enable extended drug release, which enhances the chances of intratumoral drug uptake compared to non-hydrogel-bound drugs. This analysis covers hydrophobic drug delivery vehicle types, hydrophobic drug loading techniques in hydrogels, and potential hydrogel applications in cancer therapy. Contact lenses, biosensor membranes, artificial heart linings, artificial skin materials, and drug-delivery devices are some of the applications of hydrogels [14].

Classification of hydrogels

Hydrogels are categorized based on the method used in their preparation. Homopolymeric hydrogels are manufactured from a unique monomer species and make up the basic structural unit of any polymer matrix. Homopolymers may have varying structures

conditioned on the monomer used and the polymerization method employed. In contrast, copper hydrogels consist of at least two distinct types of monomers, each with a hydrophilic component. These components can be assembled randomly, in a clog (up) arrangement, or in a staggered configuration along the polymer network's chain.

Polymeric Hydrogel (IPN Multipolymer Interpenetrating) is another characteristic of hydrogel. It comprises two autonomous cross-linked synthetic or natural polymer components in a network form. A semi-IPN hydrogel consists of two polymer components, where one of the polymers has been crosslinked while the other one has not been crosslinked [30].

Recent Trends in Hydrogel Formulation

Lowman *et al*. conducted a recent study on the application of pH-responsive complexation hydrogels in oral insulin delivery. These hydrogels are made of cross-linked copolymers of PMAA and graft chains of polyethylene glycol (P (MAA-G-EG)). Their purpose is to protect insulin from the acidic environment of the stomach and release it in the small intestine. Solid hypoglycemic effects that are dose-dependent have been observed in in-vivo oral administration studies on both healthy and diabetic rats using microparticles containing insulin and P (MAA-G-EG) [29].

Hydrogel Formulation in Buccal Delivery

Devices utilizing hydrogel can be outlined to provide medication to specific areas within the gastrointestinal tract through buccal administration. An in-situ gelling system, which contains curcumin, was created for the purpose of treating mouth candidiasis via application to the buccal cavity. The gels exhibited highly effective *in vitro* gelling as well as anti-fungal properties. Furthermore, antibiotic drug delivery systems that target the stomach were developed and utilized to treat Helicobacter pylori infection associated with peptic ulcer disease [1].

Hydrogel Formulation in Topical Antibiotics

Hydrogels are an effective vehicle for topical drug administration due to their sizeable aqueous component, promoting better drug dissolution and migration through a liquid vehicle than ointments or cream bases. They are also stable, non-sticky, easy to formulate, and have a better aesthetic value than ointments. Another advantage of hydrogels is their ability to encapsulate drugs or cells in a homogeneous material. Buchananian lanzan (BL), a beneficial tree plant from the Anacardiaceae family, has been used efficiently to treat skin diseases, swelling of glands, and cardiotoxicity. The plant extract also has wound-healing and anti-biofilm properties, which is imperative since biofilm-producing microorganisms can delay wound healing and promote resistance to commonly used topical antibiotics [39].

Hydrogel in Antimicrobial Formulation

Extensive research and development in biomedical science has led to the discovery of magnetic hydrogels, a novel class of materials. These hydrogels have shown great potential in the field of controlled drug delivery. For example, a PVA-maa hydrogel that is chemically cross-linked has been developed for the oral administration of 5-fluorouracil. Furthermore, scientists have identified a Chitosan PVA hydrogel as a viable option for creating antimicrobial formulations. A study by [17] demonstrated that a polysaccharide magnetic hybrid hydrogel can release a model drug by applying a magnetic field.

Hydrogels are a type of material that contains a substantial amount of water, making them very parallel in flexibility to usual tissue. Entrapping microbial cells within hydrogel beads has the benefit of low toxicity and can discharge growth factors and other nutrients timed to confirm appropriate tissue progress. Hydrogels have excellent transport properties and can be injected. They are also biocompatible and easy to modify [44].

Disadvantages of Hydrogels

Highly expensive hydrogels comprise a secondary dressing to secure them in place and are non-adherent. Hydrogels can lead to hypoxia, dehydration, pink-eye reactions, and lens deposition when used as contact lenses [5].

Hydrogels Technical Features

Hydrogel materials that are effective must possess several functional characteristics, which include the ability to absorb the maximum amount of saline, achieving the desired absorption rate through particle size and porosity, having the highest absorbency under load (AUL), containing low levels of soluble content and residual monomer, being affordable, having high durability and stability when swelling and stored, being biodegradable without producing toxic species, having a pH that is neutral after swelling in water, being colorless, odorless, non-toxic, and photostable [36].

Several methods can yield physically cross-linked hydrogels, which are described below.

Physical Cross-Linking

There is increasing interest in physical or reversible gels since they are easy to produce and do not require pass-linking agents, which can harm entrapped substances. A wide variety of gel textures can be achieved by carefully selecting hydrocolloids, their concentrations, and pH ranges. This area of research is currently receiving significant attention, particularly in the food industry [15]. Various methods reported in the literature to obtain physically cross-linked hydrogels include:

1. Heating/cooling a polymer solution

Hot gelatine or carrageenan solutions are cooled to form physically cross-linked gels. The gels form when helices are created and associated with each other, leading to the formation of junction zones. Carrageenan is a random coil conformation in a warm solution above the melting transition temperature. Upon cooling, it becomes rigid helical rods. In the presence of salt such as K+ or Na+, the repulsion of sulphonic groups (SO– 3) is screened, and the paired helices further combine to custom solid gels (as shown in Figure 3). Hydrogels can be obtained by simply heating polymer solutions, which causes wedge copolymerization. Such hydrogels include polyethylene oxide-polypropylene oxide and polyethylene glycol-polylactic acid hydrogel [23].

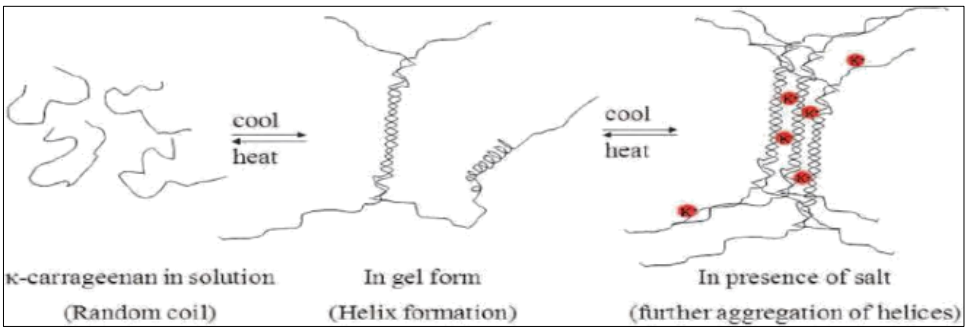

Fig 1: Upon freezing a warm carrageenan solution, helix accumulates and leads to gel formation.

(II) Ionic Interaction

Di- or tri-valent counterions are used to cross-link ionic polymers. In order to turn Na+ alginate into a polyelectrolyte solution, a multivalent ion with opposite charges, such as Ca2+ + 2Cl- (see Figure 2), is introduced, which results in the formation of a gel. Various examples of this technique include chitosan-polylysine, chitosan-glycerol phosphate salt, and chitosan-dextran hydrogels [22].

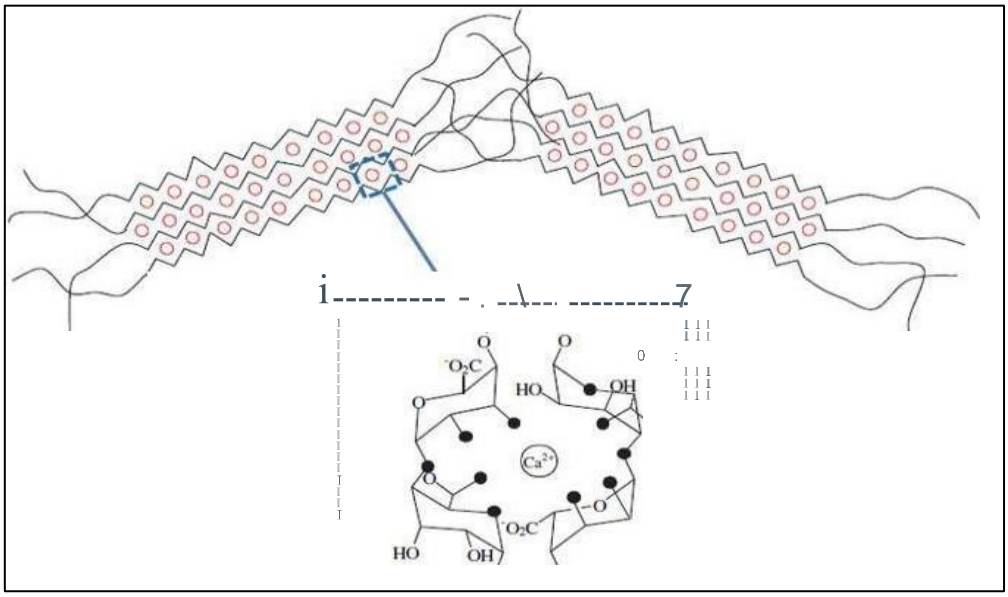

Fig 2: Ionotropic gelation by interaction between anionic groups on alginate (COO-) with divalent metal ions (Ca2+).

(III) Complex Coacervation

When a polyanion and a polycation are mixed, they can form coacervate gels. This happens because polymers with opposite charges are attracted to each other, leading to the creation of soluble and insoluble complexes. The formation of these complexes depends on the concentration and pH of the solutions. For example, if polyanionic xanthan is mixed with polycationic chitosan, a coacervate can be formed. Proteins that have a positive charge and are below their isoelectric point are more likely to combine with anionic hydrocolloids, resulting in the creation of a polyion complex hydrogel, also known as a complex coacervate. [33]

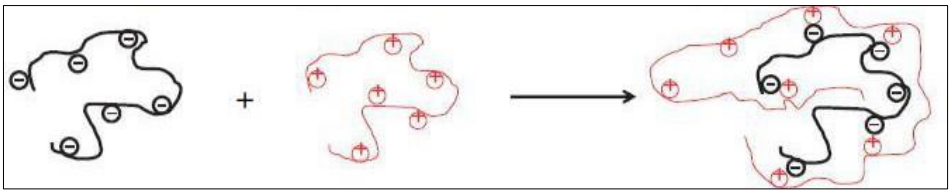

Fig 3: Complex coacervation between a polyanion and a polycation [12].

(IV) H-Bonding

Lowering the pH of an aqueous solution containing polymers with carboxyl groups can create hydrogen-bonded hydrogels. One example is a CMC hydrogel formed by adding CMC to 0.1M HCl, which replaces the sodium in CMC with hydrogen and promotes hydrogen bonding. This reduces CMC's solubility in water, resulting in an elastic hydrogel. Another type of hydrogel is the CM-chitosan hydrogel, which can be created through crosslinking in the presence of acids or polyfunctional monomers. The PEO-PAAc hydrogel is based on polyacrylic acid and

polyethylene oxide and is formed by lowering the pH to create an H-bonded gel in its aqueous solution. Molecular interactions between xanthan and alginate are used to create the combined device, causing a change in the matrix structure due to hydrogen bonding between the molecules. This results in the formation of an insoluble hydrogel network [23, 45].

(V) Maturation (Heat-Induced Aggregation)

Gum arabic can be separated into three vital fractions, namely arabinogalactan protein (AGP), arabinogalactan (AG), and glycoprotein (GP), using hydrophobic interaction chromatography. These fractions possess distinct protein contents and molecular weights. When gum arabic is subjected to heat treatment, the proteinaceous components tend to aggregate, which results in the formation of a hydrogel with excellent mechanical properties and water-binding capacity. The maturation process of gum Arabic leads to an increase in the concentration of the high molecular weight fraction (AGP) by switching the protein associated with lower molecular weight additives. This method has also been applied to other gums such as gum ghatti and *Acacia* keratosis, which are utilized in denture care.

Therefore, gum arabic plays a critical role in producing hydrogels with molecular dimensions that are precisely controlled since the agglomeration of proteinaceous components within the molecularly dispersed system present in the natural gum is the determining factor [2].

Polymer molecules having proteinaceous groups. Aggregation of proteinaceous groups on maturation

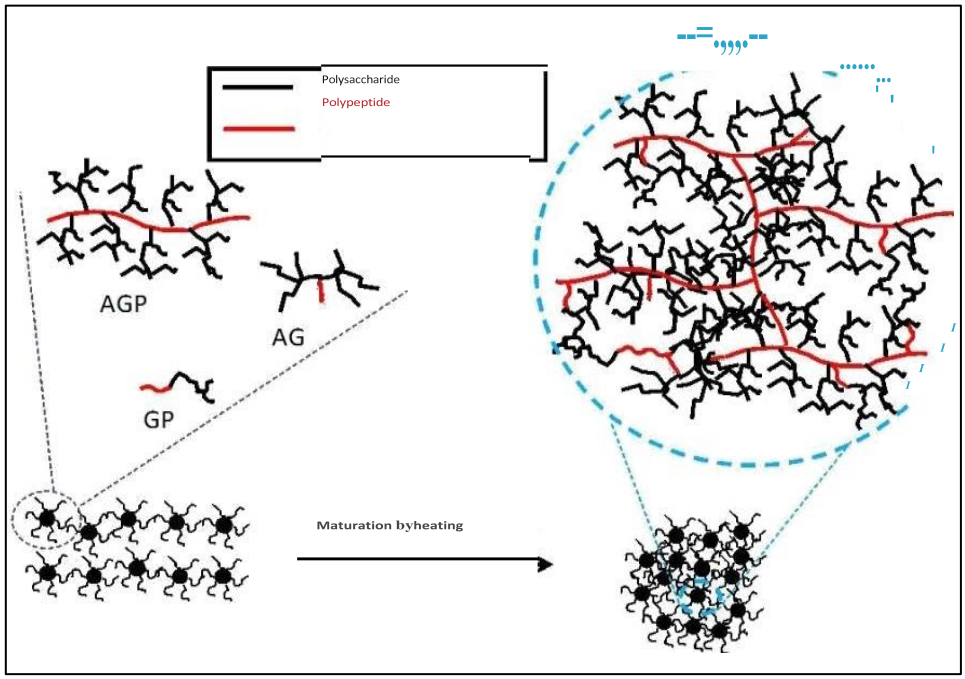

Fig 5: Maturation of gum Arabic causing the aggregation of proteinaceous part of molecules leading to pass-related hydrogel network [3].

(VI) Freeze-thawing

Via the process of freeze-thawing, a hydrogel can be created from a polymer through physical cross-linking. This mechanism involves the formation of microcrystals within the structure due to repeated freezing and thawing. Examples of polymers that can be transformed into hydrogels via freeze-thawing include polyvinyl alcohol and xanthan [19].

(VII) Poly Acrylic Hydrogel Preparation Method

Hydrogel production involves the use of various monomers, commonly acrylics. The use of acrylic acid (AA) and its sodium or potassium salts is prevalent in industrial hydrogel manufacturing. This colorless liquid has a vinegar-like smell and can dimerize into DAA. To prevent issues such as yield reduction, loss of soluble fraction, and residual monomers in the end product, manufacturers keep the amount of DAA as low as possible. To avoid dimerization, manufacturers take appropriate measures, such as timely ordering, just-in-time delivery, moisture exclusion, and temperature-controlled storage (usually around 17-18 °C), due to AA's inherent tendency to dimerize over time [48].

Optimization of Hydrogel by way of hydrogel Polymerization Technique

For hydrogel preparation, free-radical initiated polymerization of acrylic acid (AA) and its salts is commonly used with a cross-linker. The carboxylic acid groups of the product are partially neutralized before or after the polymerization step. Initiation is typically achieved through chemical means with free-radical azo or peroxide thermal dissociative species or through a reaction of a reducing agent with an oxidizing agent (redox system) [11].

The product is created by an exothermic reaction that happens quickly, resulting in a gel-like, elastic substance. Afterward, the mass is dried, and the resulting material is pulverized and sifted to achieve the desired particle size.This process can be challenging due to the problematic handling of the rubbery/solid reaction product, imprecise reaction manipulation, vague particle size distribution, and increased sol content due to hydrolytic and thermal cleavage. However, for the overall production of a hydrogel with suitable swelling properties, manufacturers often choose the cheaper and quicker solution method [16].

The DAA charge formation remains constant when water concentration increases, however, every 5°C rise in temperature doubles the rate of charge. For example, if an AA sample contains 0.5 water, the demonization rate at 20°C and 40°C would be 76 and 1672 ppm/day, correspondingly. Nevertheless, DAA can be decomposed in an alkaline atmosphere which leads to the formation of diacrylic acid and AA. These substances cannot be polymerized and remain in the hydrogel as a soluble fraction. Hydrogel synthesis primarily involves solution-reversed suspension and reversed emulsion polymerizations. Figure 6 displays a block diagram of a traditional solution polymerization system that shows the primary techniques used for hydrogel production on semipilot and industrial scales [4].

Figure 7 illustrates the key components of a real free-radical copolymerization reactor setup in a flow sheet. Monomers A and B, along with the initiator, solvent, and chain transfer agent, are continuously introduced into the system. There is a possibility that an inhibitor might enter the fresh feeds as an impurity. These feed streams are combined (flow 1) with the recycle stream (flow 2) and directed towards the reactor (flow 3), which is a well-mixed tank with a jacket. A coolant is utilized to remove the heat generated during the polymerization process. The polymer, solvent, unreacted monomers, initiator, and chain transfer agent are directed to the separator (flow 4), where the polymer, residual initiator, and chain transfer agent are separated. The unreacted monomers and solvent (flow 7) are then transported to a purge point (flow 8) to prevent the accumulation of impurities in the system. The monomers and solvent (flow 9) are stored in the recycle hold tank after the purge, which acts as a surge capacity to balance out variations in the recycle flow and composition. The effluent recycle (flow 2) is combined with the fresh feeds. [26]

(II) Optimization of Hydrogel Beads Using a Suspension Polymerization Technique

The inverse-suspension method is a flexible and versatile way to produce hydrogels that have high swelling capacity and rapid absorption kinetics. Water-soluble initiators are preferred due to their environmental friendliness compared to their oil-soluble counterparts. This method involves dissolving the initiator in the dispersed aqueous phase, allowing each particle to carry all of the reactive species and function as a micro-batch polymerization reactor. The microspherical particles produced can be easily removed from the continuous organic phase through filtration or centrifugation, and when dried, they form a free-flowing powder. Compared to the solution method, the inverse suspension system has several benefits including better control over the reaction heat removal, regulation of particle size distribution, and opportunities for adjusting the particle shape or morphology, making it an ideal method for producing hydrogel microparticles with a size range of 1 μm to 1 mm. In suspension polymerization, the monomer solution is dispersed in the non-solvent, forming small, stable droplets that are further stabilized by the addition of a stabilizer. The initiation of polymerization is done through the radicals produced by the thermal decomposition of an initiator. After formation, the microparticles undergo a thorough washing process to remove any remaining monomers, cross-linking agents, and initiators. The inverse-suspension method is a popular method for producing polyacrylamide-based hydrogels due to its ease of use and efficient removal of the hazardous acrylamide monomer residue from the polymer [49].

Evaluation procedure of hydrogel

(a) Physical characteristics

The hydrogel preparations were visually examined to evaluate pH, color, thickness, texture, uniformity, presence of granules, and phase separation.

(b) Determination of pH

The digital pH meter was used to determine the pH of the hydrogel formulations. The necessary amount of gel was dissolved in distilled water, and the electrode was then immersed in the gel components for 30 minutes until a stable reading was obtained. Moreover, consistent readings were observed. The pH was measured three times for each component, and the mean values were calculated. [27]

(c) Wash ability

The skin was coated with substances, and the subsequent amount of water required for washing was assessed manually.

(d)Extrudability examination

Collapsible metallic or aluminum tubes were used to contain the hydrogel formulations. The tubes were then compressed to release the material, and the ability of the system to be extruded was tested [50].

(e) Spreadability

To assess the spreadability of a hydrogel formula, glass slides with modern dimensions of 6×2 were chosen. The formulation was applied to one slide, and the other slide was placed on top to create a sandwich. Evenly spreading the mixture to form a thin layer was achieved by applying a weight of 100 grams on the top slide. After removing the weight, any extra formula was scraped off. The lower slide was secured, and a string that could hold a 20-gram load was attached to one end of the top slide.

Potential Applicability's of Hydrogel

The experiment involved measuring the time it took for the higher slide to move across a 6 cm gap and separate from the lower slide in the opposite direction of the weight. To ensure accuracy, six trials were conducted, and the average of the six determinations was calculated for each of the hydrogel components [43].

The formula used for measuring spreadability was S = m.L/t, where S represents the spreadability in gcm/sec, m was the weight attached to the higher slide (20 grams), l was the length of the glass slide (6cms), and t was the time in seconds that it took for the slide to move from one end to the other.

(f) Viscosity

The viscosity of the hydrogel was measured using a Brookfield digital Viscometer by filling the wide mouth area with an adequate amount of hydrogel. Spindle no. 6 was used to measure viscosity at 10 rpm and 250 °C. To ensure that the spindle of the viscometer could move freely, the hydrogel was filled in such a way that it allowed sufficient space. Before taking measurements, samples of the hydrogel were allowed to settle for 30 minutes at room temperature (25±/10 °C). [34]

(g)Drug Content

Accurately measured topical hydrogel weighing a hundred milligrams was placed in a beaker. Then, a solution of 20 ml phosphate buffer pH 7.4 was added to the beaker and mixed well.

The mixture was filtered with Whatman filter paper no. 1. One milliliter of the filtered solution was then transferred into a 10 ml volumetric flask. The flask was filled to the brim with phosphate buffer pH 7.4. Finally, the solution was analyzed using a UV spectrophotometer at λmax 275 nm. [51]

(h) Accelerated stability studies

The stability of the optimized formula was evaluated in compliance with the guidelines of the International Conference on Harmonization (ICH). The aluminum tube system underwent an extended stability test for three months, following ICH standards, at a temperature of 40 ± 2oC and relative humidity of 75 ± 5%. The samples were analyzed for pH, spreadability, drug content, and in-vitro drug release at regular intervals of one month for three months using the same method as before. Any changes in the evaluation parameters were recorded, and the tests were conducted in triplicate. The mean values along with the standard deviation were reported [35].

Discussion

Hydrogel plays a crucial role in pharmaceutical technology. This study aims to assess the use of hydrogel and the related methods. The study includes various literature reviews to comprehend how hydrogel's properties and applications are employed in drug delivery systems. The review initially discusses hydrogel as a polymer network that swells significantly with water and retains a substantial amount of water in its structure without dissolving it. The paper also covers the manufacturing technology of hydrogel, including optimized conditions and preparation methods like free radical-initiated polymerization of acrylic acid (AA) and its salts with a cross-linker. Hydrogel preparation commonly uses this method. The carboxylic acid groups of the product are partially neutralized before or after the polymerization step. The initiation process is typically chemical through free-radical azo or peroxide thermal dissociative species or via the reaction of a reducing agent with an oxidizing agent redox system. Another approach is to optimize hydrogel beads using a suspension polymerization process. Inverse suspension is a highly adaptable and versatile method to produce hydrogels with high swelling capacity and fast absorption kinetics. A water-soluble initiator is more efficient than an oil-soluble one. When the initiator dissolves in the dispersed (aqueous) phase, each particle contains all the reactive species, behaving like an isolated micro-batch polymerization reactor.

Expansion of medical research has been observed in the literature, specifically in the area of hydrogels, which are recognized for their strength and ability to self-repair due to their reversible d-stem cell. Various techniques have been employed to physically cross-link hydrogels in order to attain the desired outcomes, such as heating/cooling a polymer solution, ionic interaction, complex coacervation, hydrogel bonding, maturation, and freeze-thawing. In the physical gelation process, hot gelatine or carrageenan solutions are cooled, leading to the formation of physical gels as a result of the helix formation, association of the helices, and forming junction zones. While carrageenan in a hot solution is in a random coil conformation, it changes into rigid helical rods upon cooling. Another technique for producing physically cross-linked hydrogels is through ionic interactions, where di or trivalent counterions are added to connect ionic polymer. The principle underlying this technique is the presence of a polyelectrolyte solution with a multi-valent ion of opposite charges. Physically cross-linked hydrogels can also be created through complex coacervation, which involves mixing a poly anion with a polycation. The underlying principle of this method is that polymers with opposite charges stick together, forming a soluble and insoluble complex depending on the concentration of the respective solution. Finally, the method of H-H bonding is employed to obtain hydrogels by reducing the pH of the aqueous solution of polymer carrying carboxyl groups.

During maturation, three main fractions with distinct protein contents and molecular weights are developed. The transfer of the protein associated with lower molecular weight additives during gum maturation results in higher concentrations of the high molecular weight fraction, AGP. This technique has been used in the denture care industry with other gums such as gum ghatti and *Acacia* keratosis. The separation process is carried out using hydrophobic interaction chromatography based on protein content and molecular weight. Hydrogel manufacturing involves freeze-thawing, which leads to the formation of microcrystals in the structure. Anionic hydrogels are used in the development of smart controlled-release systems for the targeted delivery of therapeutic proteins in the large intestine. Hydrogels can be used to protect and store various drugs in hostile environments and release them at a controlled rate. Hydrogel coatings are effective in safeguarding precision components from surface damage, and hydrogel-based delivery tools are suitable for oral, ocular, epidermal, and subcutaneous applications due to their high water content. Additionally, transformer hydrogels are micro-mesostructured hydrogels that undergo a significant transformation, and have potential applications in soft-robotics, bioanalytical chemistry, regenerative medicine, and drug delivery.

When evaluating hydrogels, several key phenomena need to be considered, including the physical characteristics of the formulation, such as pH, texture, and phase separation during preparation. The washability of formulations on skin and the ease and extent of washing with water were manually tested. An extrudability study was conducted to assess the formulation's ability to be extruded. Finally, stability studies were carried out on optimized formulations in compliance with International Conference on Harmonization (ICH) guidelines.

Conclusion

Smart drug delivery systems have been developed using hydrogels, which have the potential to release drugs at specific locations in response to external stimuli such as temperature, pH, glucose or light. Hydrogels are biocompatible and biodegradable, making them useful in nanobiotechnology for controlled drug delivery. Different types of hydrogel-based networks have been created for various applications, and they can swell when in contact with aqueous solutions. A literature review is presented in this article, which includes the classification of hydrogels based on various factors, their physical and chemical properties as well as their technical feasibility for usage. It also covers the technologies involved in hydrogel production, including process design implications, block diagrams, and preparation conditions that have been optimized. Additionally, this review discusses super-porous hydrogels, a new category of hydrogel materials that can quickly swell to a large size. Different generations of super-porous hydrogels have been developed to meet specific application requirements. According to the literature survey, batch or semi-batch reactors are suitable for polymerization processes. Batch reactor variables include temperature, pressure, batch cycle time, reactant quantity, and feed

addition method. Optimization variables such as batch cycle time and reactant quantity are continuous variables with constant values for a given batch reactor system, which mainly depends on material and energy balance. Finally, there are three impellers that are known to be effective in high viscosity levels: ribbon mixers with a screw across the axis, screw mixers with four baffles, and double ribbon mixers.

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