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"Hydrogel: From Preparation To Applications – A Review On Key Properties And Formulation Techniques"

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ABSTRACT

A hydrogel is a network of hydrophilic polymer chains, similar to a colloidal gel in which water is dispersed medium. Hydrogels, whether natural or manmade, are highly absorbent polymeric networks that can contain over 90% water. Because of their high water content, hydrogels are flexible and comparable to natural tissue. The literature on this topic is growing, particularly in scientific research fields. This paper aims to evaluate the literature on hydrogel classification, physical and chemical properties, preparation methods, and technological feasibility.

KEYWORDS

Hydrogel, colloidal gel, hydrophilic, Chemical cross-linking, Polymer, Application.

INTRODUCTION

The materials of interest in this brief review are primarily hydrogels, which are polymer networks extensively swollen with water. Hydrophilic gels that are usually referred to as hydrogels are networks of polymer chains that are sometimes found as colloidal gels in which water is the dispersion medium[1-4]. Now a day's Pharmaceutical companies are developed different dosages form of drugs with higher rate of drugs release in to systemic circulation from dosage form. Tablet, capsule, injections, microspheres, suspensions, emulsions, ointments, creams, tinctures, powders, pastes, hydrogels, jellies, aerosols, nano particles and transdermal patches are some examples of dosages form with their sub categories for different route of administrations. All these dosages forms are have their own properties and advantages regarding to drug releases rate from dosages form. Most of the pharmaceutical companies today are oriented toward designing new pharmaceutical dosage forms of existing drugs rather than discovering new drug products. Utilization of the existing resource of marketed and patented drug substances with known therapeutic effects, and modification of their pharmaco-therapeutic characteristics by incorporation in suitable drug delivery system, has been the target of recent pharmaceutical development[5-8].

Functional principle of Hydrogel

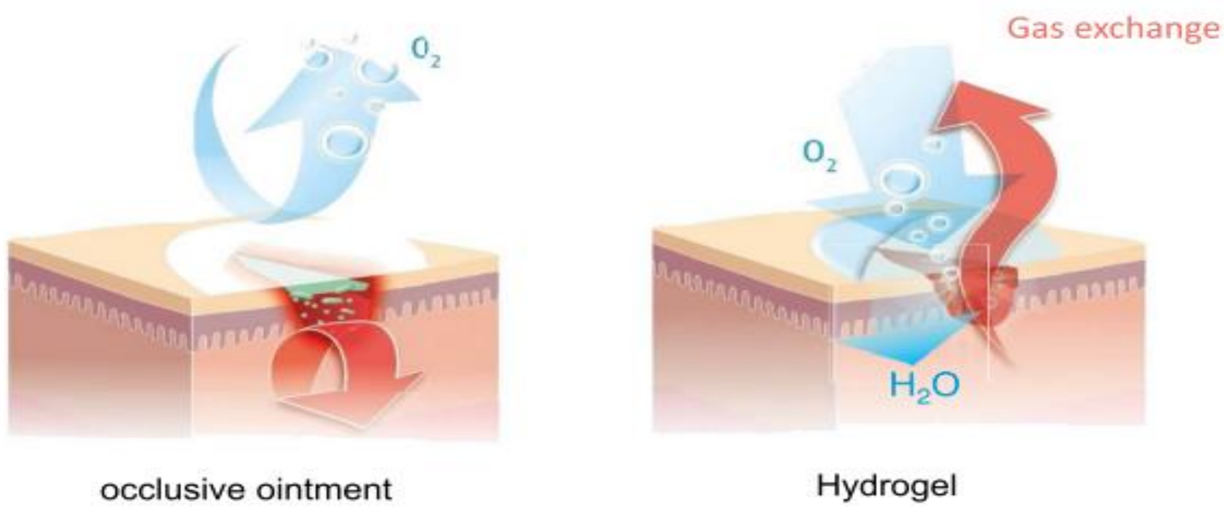

Figure 1 . In contrast to strongly occlusive bases such as Vaseline, which protects against dehydration but does not contain its own water, the hydrogel base allows extensive preservation of respiratory capacity and provides the wound with additional moisture.[33]

TYPE OF HYDROGEL

Types of hydrogel on basis of sensitivity[1]:

1. pH-Sensitive Hydrogels

- **Response**: These hydrogels swell or shrink in response to changes in pH.
- **Application**: Used in drug delivery systems where the release of the drug is triggered by the acidic or basic environment in certain parts of the body (e.g., stomach vs. intestine).
- **Example**: Poly(acrylic acid)-based hydrogels that respond to the pH of different body environments.

2. Temperature-Sensitive Hydrogels

- **Response**: These hydrogels change their swelling behavior or physical state with temperature variations. Typically, they undergo a **"sol-gel" transition** (from a liquid-like sol phase to a gel phase) at a certain temperature.
- **Application**: Often used in **drug delivery**, **tissue engineering**, and **biosensors** where temperature fluctuations are used to control the release of therapeutic agents.
- **Example**: Poly(N-isopropylacrylamide) (PNIPAM), which exhibits a lower critical solution temperature (LCST), shrinking above a certain temperature.

3. Ionic Strength-Sensitive Hydrogels

- **Response**: These hydrogels respond to changes in the ionic strength (concentration of salts) of the surrounding solution, causing swelling or deswelling.
- **Application**: Used in controlled drug delivery and biosensors where ionic interactions are critical, such as in the bloodstream where ionic conditions change.
- **Example**: Polyelectrolyte-based hydrogels that respond to salt concentrations.

4. Solvent Quality-Sensitive Hydrogels

- **Response**: Hydrogels in this category swell or shrink based on the quality (polarity) of the surrounding solvent. A good solvent (one that interacts well with the hydrogel) causes the hydrogel to swell, while a poor solvent (one with less interaction) leads to deswelling.
- **Application**: Useful in environments where solvent conditions fluctuate, such as in certain pharmaceutical or biomedical applications.
- **Example**: Polymeric hydrogels like poly(vinyl alcohol) (PVA) that change their volume based on solvent interactions.

5. Biorecognition-Sensitive Hydrogels

- **Response**: These hydrogels are sensitive to specific biological molecules (e.g., enzymes, antibodies, or antigens). They change their swelling properties or structure in response to interactions with biomolecules.
- **Application**: Used in **biosensors**, **drug delivery**, and **diagnostic applications**, where the hydrogel's response is triggered by biological signals or targets.
- **Example**: Hydrogels designed with **antibody-antigen** interactions, or **glucose-sensitive** hydrogels used for diabetes management.

6. Magnetic Field-Sensitive Hydrogels

- **Response**: These hydrogels respond to magnetic fields, usually because they are loaded with magnetic nanoparticles or other magnetic components.
- **Application**: Used in **controlled drug delivery** or **tissue engineering**, where an external magnetic field can be used to manipulate the hydrogel's behavior.
- **Example**: Hydrogels incorporating **iron oxide nanoparticles** that respond to a magnetic field for controlled release or tissue manipulation.

Types of hydrogel on basis of sensitivity :

SR.NO	SENSITIVITY TYPE	POLYMER SYSTEM	COMMENT
1	pH	poly(methacrylic acid-co-methyl methacrylate)	Hydrogel, 22/78 molar %, with two cross-linking degrees (0.3 and 0.5%)
2	Thermo	Poly (N-t butyl acryl amide-co acrylamide)	Prepared by free-radical cross linking copolymerization
3	pH	chitosan-alginate, chitosan carboxymethylcellulose sodium and chitosan-carbopol	Polyelectrolyte complexe hydrogels with prolong drug release systems using Diltiazem HCl
4	Enzyme	Poly (ethylene glycol)	Formed by Thiol-ene photopolymerization technique to fabricate protein delivery vehicles capable of enzyme responsive protein release at sites of inflammation

5	pH-thermo	poly-N-isopropylacrylamide	Formed by Electrochemically induced polymerization
6	pH	Poly (acrlyamide-co- acrylic acid)	Superporous hydrogels with fast responsive properties of system
7	IR light	N-isopropylacrylamide	IR light-responsive hydrogel was used to made liquid-based tunable microlenses
8	pH	Chitosan–Poly(vinyl alcohol)	Modified pH sensitive swelling
9	Electro	Poly dimethyl amino propyla crylamide	Prepared by either cross-linking the water-soluble polymers using radiation or chemical agents
10	Electro	chondroitin4-sulphate	Potential matrices for the electro controlled delivery of peptides and proteins

Table no 1 : Types of hydrogel on basis of sensitivity[1]

ADVANTAGES OF HYDROGELS

1. **Flexibility Similar to Natural Tissue**: Hydrogels contain a significant amount of water (typically 90% or more), which gives them a soft, flexible structure similar to the extracellular matrix of tissues in the human body. This makes them ideal for applications like tissue engineering, wound healing, and drug delivery, where compatibility with biological tissues is essential.
2. **Biocompatibility**: hydrogels can be made from natural or synthetic polymers that are non-toxic and can interact well with living cells, they are considered biocompatible. This reduces the risk of an immune response, making them safe for medical uses such as implants, scaffolds, or drug carriers.
3. **Biodegradability**: Many hydrogels can degrade naturally within the body over time, which is crucial for temporary medical applications. This eliminates the need for surgical removal and reduces the risk of long-term complications. For instance, hydrogels are used in drug delivery systems, where they gradually break down as they release the therapeutic agent.
4. **Injectability**: Hydrogels can be formulated to be injectable, allowing them to be administered minimally invasively. This is particularly beneficial in controlled drug delivery, where precise dosages are required, or in the case of injectable scaffolds for tissue regeneration.
5. **Good Transport Properties**: Hydrogels are excellent at absorbing and retaining water, and they also facilitate the movement of small molecules like nutrients, drugs, and oxygen. This makes them ideal for use in controlled drug release systems and wound dressings, where they need to support healing by allowing for moisture retention while still enabling the transport of necessary substances.
6. **Easy to Modify**: Hydrogels can be easily modified at the chemical or physical level to achieve desired properties such as mechanical strength, degradation rates, or responsiveness to environmental factors. This versatility allows for customization to meet the specific needs of different applications.
7. **Environmentally Sensitive Hydrogels**: These "smart" hydrogels can respond to external stimuli like pH, temperature, ionic strength, or the presence of specific metabolites. For example, they can release drugs in response to a change in pH (e.g., the acidic environment of a tumor) or temperature (such as fever). This adaptability makes them highly useful for targeted drug delivery and other therapeutic applications

DISADVANTAGES OF HYDROGELS

1. **Non-adherent**: Often require a secondary dressing to stay in place.
2. **Sensation of movement**: Can cause discomfort, especially in maggot therapy.
3. **Low mechanical strength**: Not suitable for load-bearing or high-stress applications.
4. **Difficult to handle**: Soft and slippery, making them challenging to apply.
5. **Expensive**: High production costs limit their accessibility and widespread use.

METHOD OF PREPARATION OF HYDROGEL :

Hydrogels can be made from both natural and synthetic polymers. Hydrogels are formed by cross-linking water-soluble linear polymers (natural or synthetic) in various ways.

- Polymer chains are linked through chemical reactions and ionizing radiation.
- Physical interactions include entanglement, electrostatics, and crystallite formation.

Hydrogels are often made from polar monomers. Polymers can be classified as natural, synthetic, or a blend of both.

1. **Bulk polymerization**

   Many vinyl monomers can be employed to create hydrogels. Bulk hydrogels can be made using several monomers. Hydrogel formulations often include a modest amount of cross-linking agent. Polymerization reactions typically start with radiation, UV, or chemical catalysts.
   In water, the glassy matrix softens and becomes more flexible[9].

2. **Solution polymerization/cross-linking**

   In copolymerization/cross-linking operations, ionic or neutral monomers are combined with a multifunctional crosslinking agent. Polymerization is begun thermally using UV radiation or a redox initiator. Wash manufactured hydrogels with distilled water to eliminate contaminants such as monomers, oligomers, cross-linking agent, initiator, soluble polymer, and more. Solvents commonly utilized for polymerizing hydrogels include water, ethanol, water-ethanol combinations, and benzyl alcohol. The polymerization process is known as "inverse suspension" technique. This approach disperses the monomers and initiators in the hydrocarbon phase as a homogeneous mixture. The size and shape of resin particles are primarily determined by the monomer solution's viscosity, agitation speed, rotor design, and dispersant type[10].

3. **Polymerization by Irradiation**

   High-energy radiations, such as gamma rays and electron beams, can be utilized to produce hydrogels from unsaturated molecules.Irradiation of aqueous polymer solutions causes the production of radicals on the polymer chains. Radiolysis of water molecules produces hydroxyl radicals, which attack polymer chains and yield macroradicals[11]

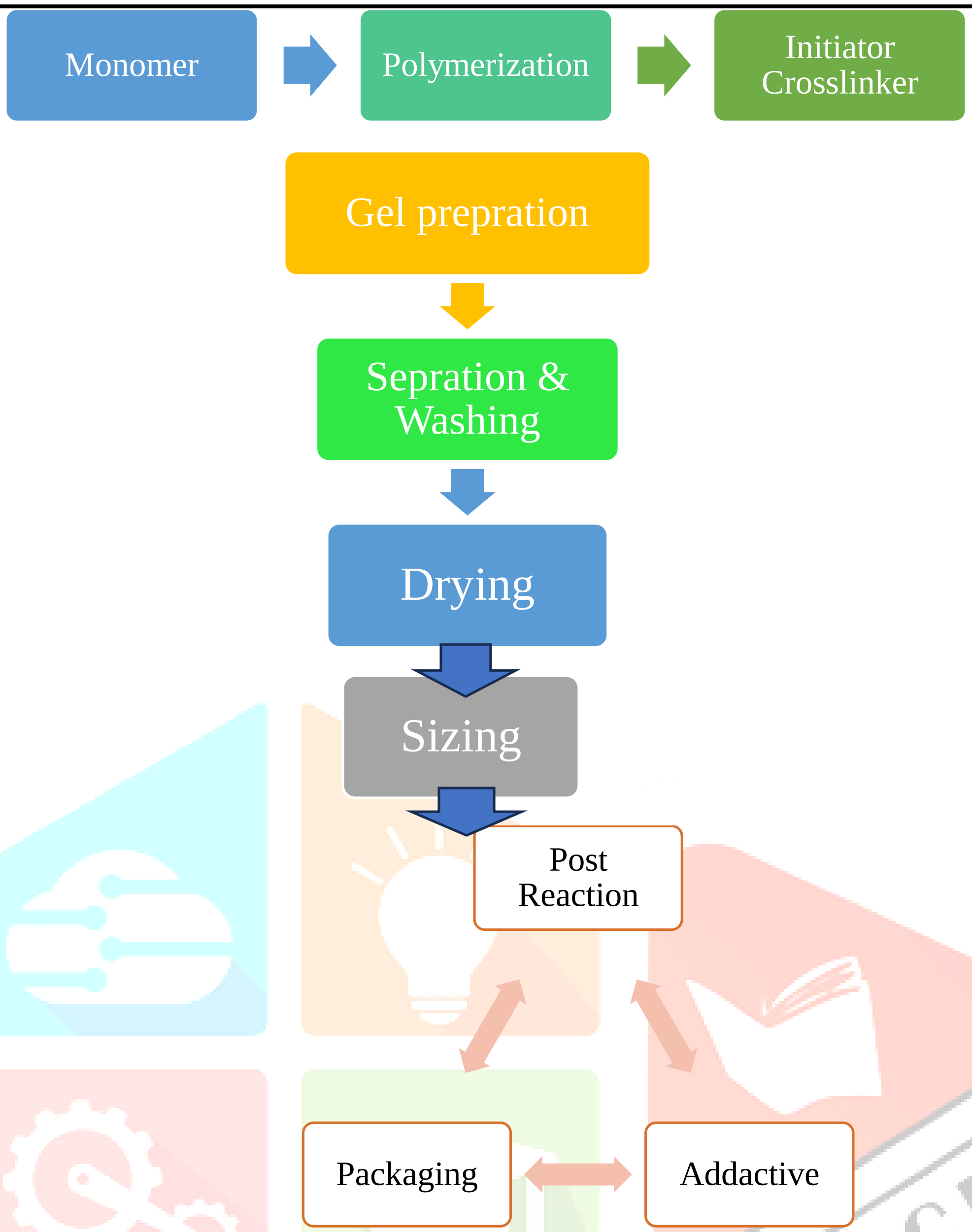

Fig 2. Hydrogel preparation block diagram solution polymerization/cross-linking procedure) [10]

DRUG RELEASE MECHANISM[12]

1) **Diffusion controlled:** The most frequent drug release method for hydrogels is diffusion controlled. Fick's law of diffusion, with constant or variable coefficients, is often used to represent diffusion-controlled release. Drug diffusivities are often measured empirically or calculated using free volume, hydrodynamic, or obstruction-based theories.
2) **Chemically controlled release** : Chemically controlled release refers to the release of molecules based on reactions within a delivery matrix. Hydrogel delivery techniques often involve polymer chain cleavage by hydrolytic or enzymatic degradation, as well as reversible or irreversible reactions between the polymer network and the medication. Hydrogel surface or bulk erosion can affect medication release rate. Incorporating drug-binding moieties into hydrogels may affect drug release rate due to binding equilibrium. Chemically regulated release can be further classified based on the chemical reaction that occurs during drug release. Typically, the breakdown of pendant

chains, surface erosion, or bulk-degradation of the polymer backbone can release encapsulated or tethered medications

3) **Swelling-controlled release** : Swelling-controlled release happens when the drug diffuses quicker than the hydrogel swelling. Modeling of this mechanism often involves releasing molecules at the junction of inflated hydrogels' rubbery and glassy phases, with shifting boundaries.

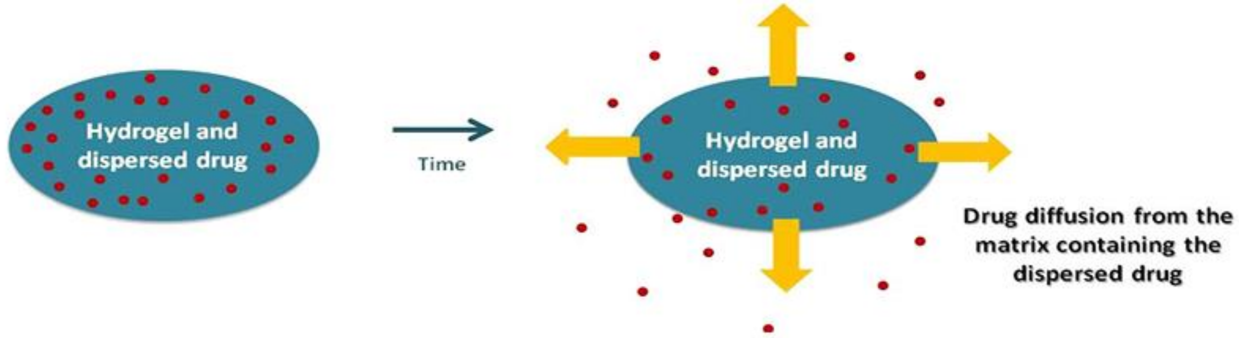

Fig 3 : Scheme of drug release through a hydrogel membrane in a reservoir system [12]

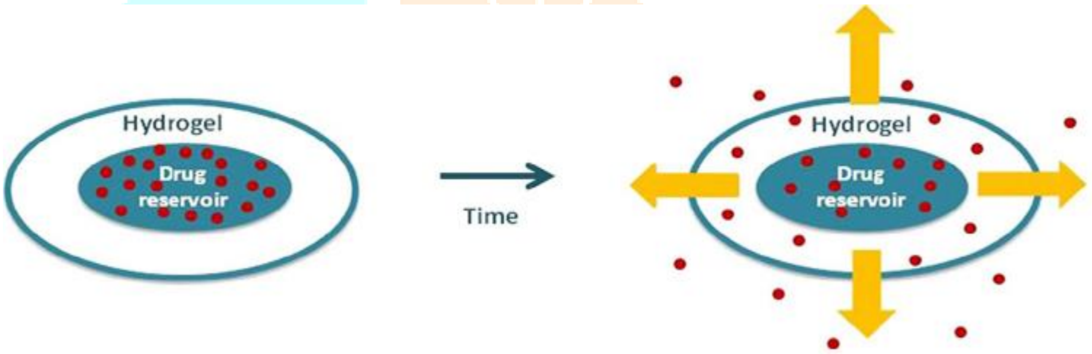

Fig 4 : Drug release from matrix systems. [12]

HYDROGEL-BASED PRODUCTS ON THE MARKET [29]

Product	Hydrogel composition	Indication	Product Manufactured by/Marketed by	Review	References
Smart C Hydrogel	Liquid Poly(acrylic acid) (oxypropylene , co oxyethylene) glycol.	Used for developmet of ophthalmic, buccal, nasal, vaginal and transdermal	MedLogi Global™ (Plymouth, UK)	Mucoadhesive composition that undergoes sol–gel transformation at body temperature	http://www medlogic.com. Aqua
Aquamere™	Interpolymers of PVPand PVPgrafted copolymers with urethane	Skincare, topical and oral drug delivery	Hydromer (Somerville, NJ, USA) Inte		http://www. hydromer.com
SQZ Gel oral release system	Chitosan and polyethylene glycol	Hypertension	Macromed (Sandy, UT, USA)	pH-Sensitive, once a-day tablet of	http://www. macromed.com

				Dilteazem Hydrochloride	
Cervidil® vaginal (PGE2)	Poly(ethylene oxide) and urethane	Initiation and/or continuation of cervical ripening (at or near term	Controlled Therapeutics, UK; marketed by insert Forest Pharmaceuticals St Louis, MO, USA)	Product contains 10 mg Dinoprostone and exhibits in vivo release rate of ~0.3 mg h–1	http://www btgplc.com

TABLE NO 2 : HYDROGEL-BASED PRODUCTS ON THE MARKET [29]

CHARACTERIZATION OF HYDROGELS :

1. **pH** - The pH of hydrogels is tested using a digital pH meter. The pH meter must be calibrated before use[13].
2. **Scanning Electron Microscopy (SEM)** provides information on sample composition, surface topography, and electrical conductivity. SEM magnification can be adjusted by up to 6 orders of magnitude, from 10 to 500,000 times.
3. **Fourier Transform Infrared Spectroscopy** is a valuable technique for detecting the chemical structure of substances. The theory behind this method is that chemical bonds in a substance can absorb infrared light at specific frequencies[14].
4. **X-ray diffraction** Diffraction analysis is used to determine crystalline or amorphous properties. It determines whether polymers maintain their crystalline structure or deform after pressurization. Diffraction analysis is a prominent method for studying the morphology of hydrogels.
5. **In-vitro drug release studies** are conducted using hydrogels, which are swollen polymeric networks that contain drug molecules. These studies aim to understand the mechanism of release over time. The parameters are matched with the standard plot to determine the equivalency of medication solutions
6. **Rheology** The viscosity of hydrogels is measured using a cone plate viscometer at 4ºC. This viscometer is highly specific for determining viscosity. Viscosity can be calculated using the angle of repose, height, and length equation[15].
7. **The spreadibility** study apparatus consisted of a wooden block with scale, two glass slides, and a pan attached on a pulley. To obtain equal thickness, excess formulation was placed between two glass slides and a weight of 100 grams was placed on the upper slide for 5 minutes[17]. Weight can be added, and the time it takes to separate the two slides was used to calculate spreadability.

   $S = (m \times l) / t$

   Where,

   S = spreadibilty,

   m = weight tied to upper slide,

   l = glass slide length,

   t = time

8. **Skin irritancy tests** are performed on rabbits. The preparation was applied to two rabbits, and the area was covered with gauze or bandages. After 24 hours, remove the formulation and inspect for edema and erythema. Average irritation scores are calculated as the sum of erythema and edema reaction values divided by the time period[18].

❖ Hydrogels and their application in controlled drug release

Applications	Polymers
Wound care	polyurethane, poly (ethylene glycol), poly (propylene glycol) poly (vinyl pyrrolidone), polyethylene glycol and agar [30]
Drug delivery, pharmaceuticals	poly (vinyl pyrrolidone) starch, poly (vinyl pyrrolidone), poly (acrylic acid)
Dental materials	Hydrocolloids (Ghatti, Karaya, Kerensis gum) [31]
Tissue engineering, implants	Hyaluronan
Injectable polymeric system	Hairpin peptide
Technical products	poly (vinyl methyl ether), poly (N-isopropyl acryl amide) [32]

Table. No 3 : Pharmaceutical Applications of hydrogels types of polymers

APPLICATIONS :

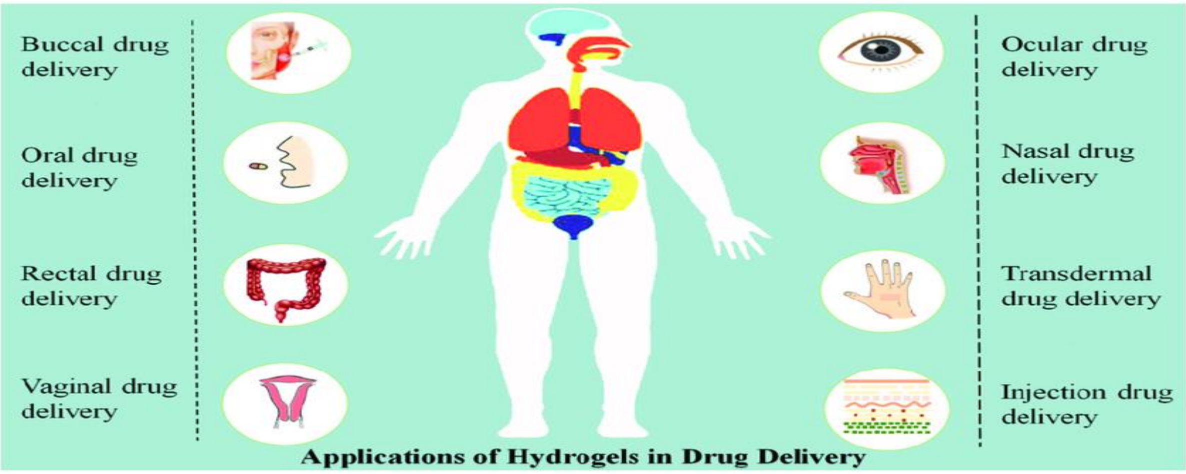

Fig 5 : Applications of hydrogels in Drug Delivery

1**. Wound healing**: The cross-linked nature of hydrogels allows them to store water and drugs. Because of their propensity to keep water, they can hold and maintain wound exudates. Polyvinyl pyrrolidine or polyacrylamide gel made up of 70-95% water[19-20].

2. **Colon-Specific Hydrogels**: Because of the high concentration of polysaccharide enzymes in the colon region of the GI, colon-specific hydrogels of polysaccharide were developed. Dextran hydrogel is designed for colon-specific medication delivery[21].

3. Drug delivery in the GI tract: Hydrogels are used to deliver medications to particular sites in the GIT. Drugs loaded with colon-specific hydrogels exhibit tissue specificity and change in pH, leading to breakdown due to enzymatic action[21].

4. **Oral drug delivery:** Hydrogels are used to treat disorders of the mouth, including stomatitis, fungal diseases, periodontal disease, viral infections, and malignancies[22].

5. Transdermal Delivery: Hydrogel-based devices can deliver drugs via transdermal routes. Hydrogel-based formulations are being tested for transdermal iontophoresis to improve product permeation, including hormones and nicotine[23].

6. **Gene Therapy :** Hydrogel composition changes enable targeted delivery of nucleic acids to specific cells for gene therapy. Hydrogels have potential for treating various disorders, both hereditary and acquired[24].

7. Tissue Engineering: Micronized hydrogels transport macromolecules into the cytoplasm of antigen-presenting cells. Natural hydrogels utilized in tissue engineering include agarose, methylcellulose, and other naturally produced materials[25-26].

9. **Ocular drug delivery**: Hydrogels are most widely used in ocular drug delivery system. Hydrogel show Controlled or sustain release in order to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at its site of action, decreasing the dose required or providing uniform drug delivery[27-28]

Conclusion

continues by underlining the relevance of hydrogels in a wide range of fields, including medicine, pharmaceutical delivery, tissue engineering, and applications in the environment. It emphasizes that the creation of hydrogels involves a full understanding of its important properties, including as swelling conduct, durability, biocompatibility, and biodegradability, since they are essential for their effectiveness in certain applications. Furthermore, the research stresses the role of formulation procedures such as crosslinking, mixing, and modification in tailoring hydrogel characteristics to specific needs. Researchers may enhance the functioning of hydrogels by altering their structure and composition, making them suitable for a wide range of novel applications. Finally, the study suggests ongoing research to address hydrogel composition challenges such as improving mechanical stability, regulating swelling behavior, and guaranteeing security and effectiveness in biomedical applications. Hydrogels have a bright future ahead of them, due to advancements in nanotechnologies, smart hydrogels, and multipurpose composite that will allow new and enhanced applications.

References:

1. Caliari, S. R. & Burdick, J. A. A practical guide to hydrogels for cell culture. Nat. Methods 13, 405–414 (2016).

2. Lin, W. et al. Cartilage-inspired, lipid-based boundary-lubricated hydrogels. Science 370, 335–338 (2020).

3. Zheng, L. et al. Intensified stiffness and photodynamic provocation in a collagenbased composite hydrogel drive chondrogenesis. Adv. Sci. 6, 1900099 (2019).

4. Contessotto, P. et al. Elastin-like recombinamers-based hydrogel modulates post-ischemic remodeling in a non-transmural myocardial infarction in sheep. Sci. Transl. Med. 13, eaaz5380 (2021).

5.Shakti Dwivedi*, Pankaj Khatri, Gilhotra Ritu Mehra and Vikash Kumar. Hydrogel - A Conceptual Overview, International Journal of Pharmaceutical & Biological Archives, 2011; 2(6):1588-1597.

6. Kim B, Peppas NA. Poly(ethylene glycol)-containing hydrogels for oral protein delivery applications. Biomed Microdevices, 2003; 5: 333-341Jagur-Grodzinski Polymeric gels and hydrogels for biomedical and pharmaceutical application. Polymers for Advanced Technology, 2009; 21: 27-47.

7.Cascone MG, Lazzeri L, Sparvoli E, Scatena M, Serino LP, Danti S. Morphological evaluation of bioartificial hydrogels as potential tissue engineering scaffolds. J Mater Sci Mater Med, 2004; 15: 1309-1313.

8. Li S, Liu X. Synthesis, characterization and evaluation of semi-IPN hydrogels consisted of poly(methacrylic acid) and guar gum for colon-specific drug delivery. Polym Adv Technol, 2008; 19: 371-376.

9.Sing SK, Dhyani A, Juyal D. Hydrogels: Preparation, characterization and Applications. The Pharma Innovation journal. 2017; 6(6): 25-32.

10. . Saini K, Preparation method, Properties and crosslinking of hydrogel: a review. PharmaTutor. 2016; 5(1): 27-36.

11. . Siddeswara M, Purushothaman M, Kumar MP, Raja MS, Yasmin S, Swathi R. Formulation and Evaluation of Desvenlafoxacine Succinate Hydrogel. International Journal of Current Trends in Pharmaceutical Research. 2016; 4(5)

12. Mallikarjuna C, Baviskar VH, Kumar M, Monica R, Bolla SP. A Review on Hydrogel- A Novel carrier. Pharma Tour. 2006; 2 (6): 42-51.

13. Rathod PD, Dabke SP, Safaya MA. Development Of pH Sensitive Hydrogel for Intestinal Delivery of Amoxicillin Trihydrate using Carbopol-PEG400, American Journal of Pharmacy and Health Research. 2015; 3 (2).

14. Gulrez SKH, Assaf S, Phillips G. Hydrogels: Methods of Preparation, Characterization and Applications. Glyn O Phillips Hydrocolloids Research Centre Glyndwr University, Wrexham United Kingdom.

15. Monica AS, Gautami J. Design and Evaluation of Topical Hydrogel Formulation of Diclofenac Sodium for Improved Therapy. International Journal of Pharmaceutical Science and Research. 2014; 5(5): 1973-80.

16. Kumari K, Sara UVS, Sachdeva M. Formulation and Evaluation of Topical Hydrogel of Mometasone Furoate using different polymers. International Journal of Pharmaceutical and chemical sciences. 2013; 2(1).

17. Chaurasiya N, Chakraborthy GS. Formulation and Evaluation of Herbal Hydrogel from Hibiscus Rosa-sinensis. International Journal of Current Pharmaceutical Research. 2014; 6(1).

18. Aulton M. Aulton‟s Pharmaceutics, The Design and Manufacture of Medicines. 3rd ed., Churchill Livingstone Elsevier; 2007: 601, 602.

19. Lugao AB, Rogero SO, Malmonge SM. Rheological behaviour of irradiated wound dressing poly (vinyl pyrrolidone) hydrogels. Radiat Phys Chem, 2002; 63: 543-546.

20.Wang M, Xu L, Hu H, Zhai M, Peng J, Nho Y et al. Radiation synthesis of PVP/CMC hydrogels as wound dressing. Nucl Instrum Methods Phys Res, 2007; 265: 385-389.

21.KS. PEG hydrogels for the controlled release of biomolecules in regenerative medicine. Pharm Res, 2009; 26: 631-643.

22.Abraham GA, de Queiroz AAA, San Roman JS. Hydrophilic hybrid IPNs of segmented polyurethanes and copolymers of vinylpyrrolidone for applications in medicine. Biomaterials, 2001; 22: 1971-1985.

23.Christensen L, Breiting V, Vuust J, Hogdall E. Adverse reactions following injection with a permanent facial filler polyacrylamide hydrogel (aquamid): causes and treatment. Eur J Plast Surg, 2006; 28: 464-471.

24.Christensen L, Breiting V, Vuust J, Hogdall E. Adverse reactions following injection with a permanent facial filler polyacrylamide hydrogel (aquamid): causes and treatment. Eur J Plast Surg, 2006; 28: 464-471.

25.Jia and K.L. Kiick Hybrid multicomponent hydrogels for tissue engineering. Macromolecular Bioscience, 2009; 9: 140-156.

26.Tabata Biomaterial technology for tissue engineering applications, Journal of the Royal Society, Interface, 2009; 6: 311-324.

27.Dubey A, Prabhu P. Formulation and evaluation of stimuli-sensitive hydrogels of timolol maleate and brimonidine tartrate for the treatment of glaucoma. International Journal of Pharmaceutical investigation.2014; 4 (3).

28.Kopecek Hydrogels: From soft contact lenses and implants to selfassembled nanomaterials. Journal of Polymer Science, 2009; 47: 5929-5946.

29. Lalita Chauhan1, Prerna Thakur, Sheetal Sharma, Hydrogels: A review on classification, preparation methods, properties and its applications, Indo American Journal of Pharmaceutical Sciences, Volume 6, Issue 6, 2019, 13490-13503

30. Chauhan S, Harikumar SL, Kanupriya. Hydrogels, A Smart Drug Delivery System, International Journal of Research in Pharmacy and Chemistry. 2012; 2(3):604615.

31. Rosiak JM, Yoshii F. Hydrogels and their medical applications, Nuclear Instruments and Methods in Physics Research B, 1991; 151:56-64.

32. Rosiak JM, Ulanski P, Zeinicki R. Hydrogels for biomedical purposes, Nuclear Instruments and Methods in Physics Research. 1995; 105:335-339.

33. M.S. Vasconcelos, T.F.G. Souza, I.S. Figueiredo, et al., A phytomodulatory hydrogel with enhanced healing effects, Phytother Res. 32 (4) (2018 Apr) 688–697

Iizawa T, Taketa H, Maruta M, Ishido T, Gotoh T, Sakohara S. Synthesis of porous poly (N-isopropylacrylamide) gel beads by sedimentation polymerization and their morphology. J Appl Polym Sci, 2007; 104: 842-850.

Gong CY, Shi S, Dong PW, Kan B, Gou ML, Wang XH et al. Synthesis and characterization of PEG-PCL-PEG thermosensitive hydrogel. Int J Pharm, 2009; 365: 89 99. 9. Lin CC, Anseth

Christensen L, Breiting V, Vuust J, Hogdall E. Adverse reactions following injection with a permanent facial filler polyacrylamide hydrogel (aquamid): causes and treatment. Eur J Plast Surg, 2006; 28: 464-471.

Thomas V, Yallapu MM, Sreedhar B, Bajpai SK. A versatile strategy to fabricate hydrogel-silver nanocomposites and investigation of their antimicrobial activity. J Colloid Interface Sci, 2007; 315: 389-395.

Zhang JT, Bhat R, Jandt KD. Temperature-sensitive PVA/PNIPAAm semi-IPN hydrogels with enhanced responsive properties. Acta Biomater, 2009; 5: 488-497.

Murthy PSK, Murali Mohan Y, Varaprasad K, Sreedhar B, Mohana Raju K. First successful design of semi-IPN hydrogel-silver nanocomposites: a facile approach for antibacterial application. J Colloid Interface Sci, 2008; 318: 217-224.

NILIMANKA DAS* PREPARATION METHODS AND PROPERTIES OF HYDROGEL: A REVIEW, International Journal of Pharmacy and Pharmaceutical Sciences, 2013; 3(5).

3.Kopecek and J. Yang Review, Hydrogels as smart biomaterials. Polymer International, 2007; 56: 1078-1098.

7. Cretu A, Gattin R, Brachais L, Barbier-Baudry D. Synthesis and degradation of poly (2 hydroxyethyl methacrylate)-graft-poly (ε-caprolactone) copolymers. Polym Degrad Stab, 2004; 83: 399-403.

18. Zhang YX, Wu FP, Li MZ, Wang EJ. pH switching on-off semi-IPN hydrogel based on cross-linked poly(acrylamide-co-acrylic acid) and linear polyallyamine. Polymer, 2005; 46: 7695-7700.

20. Gils PS, Ray D, Sahoo PK. Designing of silver nanoparticles in gum arabic based semi IPN hydrogel. Int J Biol Macromol, 2010; 46: 237-244.

21. Ju HK, Kim SY, Kim SJ, Lee YM. PH/temperature-responsive semi-IPN hydrogels composed of alginate and poly(N-isopropylacrylamide). J Appl Polym Sci, 2002; 83: 1128-1139.

23. Lu S, Liu M, Ni B, Gao C. A novel pH- and thermo-sensitive PVP/CMC semi-IPN hydrogel: Swelling, phase behavior, and drug release study. J Polym Sci Part B: Polym Phys, 2010; 48: 1749-1756.

24. Lipatov YS. Polymer blends and interpenetrating polymer networks at the interface with solids. Prog Polym Sci, 2002; 27: 1721-1801.

25. Muniz EC, Geuskens G. Polyacrylamide hydrogels and semi-interpenetrating networks (IPNs) with poly(N-isopropylacrylamide): mechanical properties by measure of compressive elastic modulus. J Mater Sci - Mater Med, 2001; 12: 879-881.

26. Zhang XZ, Zhou RX. Synthesis of temperature-sensitive poly (Nisopropylacrylamide) hydrogel with improved surface property. J Colloid Interface Sci, 2000; 223: 311-313.

27. Mohamadnia Z, Zohuriaan-Mehr MJ, Kabiri K, Jamshidi A, Mobedi H. pH-sensitive IPN hydrogel beads of carrageenan-alginate for controlled drug delivery. J Bioact Compat Polym, 2007; 22: 342-356.

28. Yin L, Fei L, Cui F, Tang C, Yin C. Superporous hydrogels containing poly(acrylic acid co-acrylamide)/O-carboxymethyl chitosan interpenetrating polymer networks. Biomaterials, 2007; 28: 1258-1266.

29. Li S, Yang Y, Yang X, Xu H. In vitro degradation and protein release of semi-IPN hydrogels consisted of poly (acrylic acid-acrylamide-methacrylate) and amylase. J Appl Polym Sci, 2007; 105: 3432-3438.

30. Chivukula P, Dusek K, Wang D, Duskova-Smrckova M, Kopeckova P, Kopecek J. Synthesis and characterization of novel aromatic azo bond-containing pH-sensitive and hydrolytically cleavable IPN hydrogels. Biomaterials, 2006; 27: 1140-1151.

31. Alvarez-Lorenzo C, Concheiro A, Dubovik AS, Grinberg NV, Burova TV, Grinberg VY. Temperature-sensitive chitosan-poly (N-isopropylacrylamide) interpenetrated networks with enhanced loading capacity and controlled release properties. J Controlled Release, 2005; 102: 629-641.

32.

33. Liu M, Su H, Tan T, Synthesis and properties of thermo and pH-sensitive poly(N isopropylacrylamide)/polyaspartic acid IPN hydrogels. Carbohydr Polym, 2012; 87: 2425-2431.

34. Matricardi P, Pontoriero M, Coviello T, Casadei MA, Alhaique F. In situ cross-linkable novel alginate-dextran methacrylate IPN hydrogels for biomedical applications: mechanical characterization and drug delivery properties. Biomacromolecules, 2008; 9: 2014-2020.

35. Iwai K, Hanasaki K, Yamamoto M. Fluorescence label studies of thermo-responsive poly(N-isopropylacrylamide) hydrogels. J Luminescence, 2000; 1289: 87-89.

36. Grassi M, Sandolo C, Perin D, Coviello T, Lapasin R, Grassi G. Structural characterization of calcium alginate matrices by means of mechanical and release tests. Molecules, 2009; 14: 3003-3017.

37. Bryant SJ, Nuttelman CR, Anseth KS. Cytocompatibility of UV and visible light photoinitiating systems on cultured NIH/3T3 fibroblasts in vitro. J Biomater Sci Polym Ed, 2000; 11: 439-457.

38. Grassi M, Sandolo C, Perin D, Coviello T, Lapasin R, Grassi G. Structural characterization of calcium alginate matrices by means of mechanical and release tests. Molecules, 2009; 14: 3003-3017.