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A REVIEW: HYDROGEL IN TOPICAL DRUG DELIVERY

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ABSTRACT

Topical drug delivery is the best and special route for local and systemic delivery of therapeutic agent due to its advantages and affordability. Conventional dosage forms were not able to give quick action to the desired area or system. At this stage, novel formulation like hydrogel comes into existence. Hydrogels are cross-linked polymeric three dimensional structure of hydrophilic group that can swell and shows it action due to environmental changes. Though, determining the absorption of drug at the site of action or skin layer by using topical preparations or product is a big task for researcher. Release of drug via topical route symbolize a most suitable and novel approach. Conventional topical dosages forms have not provide any evidence to be useful in topical drug delivery. Novel drug delivery systems show a great potential for topical delivery. To defeat the problems related with conventional delivery devices, polymeric gels such as hydrogels have been recommended. Hydrogels have been extensively used as the transporter for drug delivery systems. These biomaterials have increase interest due to their characteristics like swelling in aqueous solution, pH and temperature sensitivity and biocompatibility. The objective of this review article to highlights the classification of hydrogel, their advantages, disadvantages, preparation method of hydrogel, characterization of hydrogel and application of hydrogels. This review disclose the convenience of hydrogel as a topical drug delivery systems used in the body by the ophthalmic route, rectal route, vaginal route and skin.

KEYWORDS: Hydrogels, Topical drug delivery, skin, Biocompatibility.

INTRODUCTION

The first synthetic Hydrogels was synthesized of by Wichterle and Lim in 1954.[1] The hydrogel used in food additives,[2] pharmaceuticals,[3] biodegradable implants[4] tissue engineering and regenerative medicines,[5] diagnostics,[6] cellular immobility[7], separation of bio-molecules or cells[8] and barrier materials to regulate biological adhesions,[9] Biosensor devices and drug transporter.[10] Furthermore the constantly increasing variety of useful monomers and macromeres expand its applicability. Ionic interaction and hydrogen bonding helps in cross linking of polymeric material.[11] As well as it provide crucial mechanical power and integrity to the hydrogels.[12] Thus, hydrogels can absorb water practically 15-25 times its molecular weight and consequently turn into swollen material.[13] Some examples of Hydrogels include contact lenses,[14] wound dressing,[15,16] super-absorbents.[17-19]

Recently hydrogels have increase significant interest. Hydrogels are 3D structure of cross-linked polymer network that are responding after environmental changes such as (pH, temperature, ionic strength, and presence of enzyme etc.) and swell up. In this state, they are flexible, soft and rubbery in nature, similar to the living tissue which shows outstanding biocompatibility.[20] That's why these biomaterials are broadly used in various fields of pharmaceutical and biomedical engineering.[21] Combination of polymers showed better performance than the individual polymers and the range of application has been extended. Carbohydrate based polymer mix is one of best example and being investigate to develop controlled release formulations.[22]

With current study in highly developed drug delivery formulations to give stable and economical drug delivery systems, the main focus is on hydrogels which are identified to decrease the problems associated with conventional dosage forms which need a biocompatible, suitable and stable drug delivery system for small molecules such as Non-steroidal anti-inflammatory drugs or large molecules such as proteins and peptides.[23-24] Fundamentally, hydrogels are net-like, hydrophilic, polymeric networks able to absorb huge quantity of water or biological fluids.[25-26] These networks structure are made up of homo-polymers or co-polymers.[27-33] These hydrogels show a thermodynamic compatibility

with water which become swollen in aqueous medium.[34-35] Now-a-days utilization of hydrogels has been increases due to their important characteristics like swelling in aqueous medium, pH and temperature sensitivity or sensitivity towards other stimuli. Hydrogels have been recognized to act as drug protectors, especially for peptides and proteins.[36]

Topical delivery involves absorption of drug from the formulation or preparation into the body. This is the best route used to provide accurate quantity of medicine reaches into the body where they are needed. Skin is the main route of the topical drug delivery to treat skin disease, or disinfection of the skin. In current years, the transdermal route has been used as a potential site for the systemic/localized delivery of drugs. Hydrogel is a gel in which the water is a main component and these hydrogels are produced by the cross-linking of polymers that are water-insoluble. They absorb considerable quantity of aqueous solutions, and therefore have high water content. Groups of polymer chain of hydrophilic gels are typically called as hydrogels are group of polymer chains.

Local application of curative agents either to the skin, or systemic circulation after passage through the skin, provides many advantages over oral and injectable drug delivery systems. These possible advantages include bypass hepatic metabolism, improved patient compliance and no difficulty on application to the skin.[37] The most important benefit of topical delivery system is that it has capability to transport drugs to a particular site (local action). It gives utilization of drugs with short biological half-life and narrow therapeutic window to increase the duration of action.[38] However, in many instances, oral administration is inappropriate when the drug go through considerable degradation in the gastrointestinal tract (GIT) or is metabolized to a high degree through the first pass effect in the liver. Topical formulations such as ointments, which can solublize large amount of hydrophobic agents, are oily and gritty as a result making the formulation unsuitable for patients. An adequate amount of a therapeutic agent must be loaded into the vehicle to make sure an enough concentration gradient between the formulation and the skin, in order to achieve sufficient release of the drug into the skin.[39,40] Topical patches do not have the ability to release the whole amount of the drug into the skin, and large amount of drug are wasted after removing the patch from the skin. The formulation form a protective layer over the skin after placing on skin, by this means fixing the medicament of the formulation in a matrix of the polymer.[41] In present scenario hydrogels are extensively used in drug delivery systems due to their significant physical and chemical properties such as controllable and prolonged release of drugs in the body.[42]

Possible benefits of topical drug delivery

1. Drug can be distributed for long duration of time at a steady rate.
2. Drug can by-pass hepatic first pass metabolism.
3. Release of drug can be suspended by termination of the device.
4. It is stable and cost-effective drug delivery systems.

Skin

Anatomy and physiology of skin

Skin is the most important tissue of the body which covers the body externally. Skin is protecting the internal organ through external environmental microbes and other elements. It controls body temperature and water loss and provide the feelings of touch, warm, and cold. In the topical drug delivery, the drug either pass through stratum corneum (SC) or go through hair follicles to reached its site of action. In the adult, skin covers an area between 1.5 to 2.0 square meters.

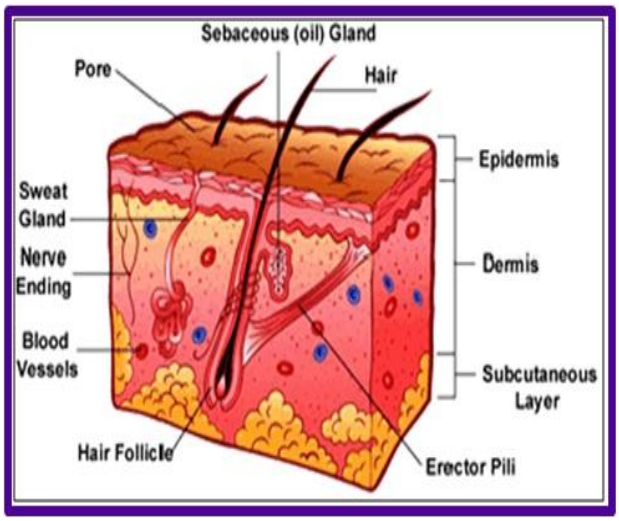

Fig. 1: Anatomy of skin.

Skin has consist three layers

1. Epidermis: These layers of skin are outmost layer of skin which provides the waterproof barrier. It is composed the keratinized stratified squamous epithelium tissue and contains the four principle type of cells: keratinocytes, melanocytes, Langerhans cells, Markel cells. Keratinocytes are produced protein keratin so as to defend the skin and tissues from high temperature, germs, and other chemical substances. About 8% of the epidermal cells are melanocytes which produce melanin pigments. Melanin is a yellow-red and black-brown pigment that gives skin colors and absorbs dangerous ultra-violet light. Epidermis has five layers – Stratum basale, stratum spinosum, stratum granulosum, stratum lucidum and thick stratum corneum, this is called thick skin where is thin skin have only four layer stratum lucidum are absence and thick stratum corneum replace by thin stratum corneum.

2. Dermis: It is the deeper part of skin mainly composed connective tissue, blood vessels, nerve, hair follicles, and gland. Dermis can be divided into papillary region and a reticular region. The papillary region makes up one fifth of entire layer. It consist areolar connective

tissue. Its exterior region is significantly increased by tiny finger like structure called dermal papillae. The reticular region are connected to the subcutaneous layer, consist of fibroblasts, bundle of collagen, and some elastic fibers. Collagen and elastic fibers are provide the skin with strength, extensively and elasticity.

3. **Hypodermis:** Deep layer of dermis or subcutaneous layer of skin is called hypodermis. Actually it is not a part of skin. Hypodermis layer consist of areolar and adipose tissues.

Accessory structure of the skin: Hair, skin gland, and nails– developed from embryonic epidermis. The hair and nails are protect the body and sweat gland are help the regulate body temperature.

Hydeogel

Definition

Hydrogels are defined as net-like three dimensional structure made up of hydrophilic homo-polymers or copolymers. They are making insoluble due to cross-linking by chemical bonds, or other cohesive forces such as ionic interaction, hydrogen bonding, or hydrophobic interaction. They do not change its polymeric structure even after being deformed for a very long time due to its elastic nature. Hydrogels are highly absorbent (can contain over 90% of water). Due to high water content, hydrogel swell up and it is able to give an improved sensitivity for skin in contrast to ointment and patches. Hydrogel are also well-known as intelligent gels or smart hydrogels. These gels have an ability to accept, transmit or process a stimulus, and react by showing a useful effect. They can recognize the existing stimulus and respond by showing alteration in their physical or chemical performance, consequential in the liberation of drug in a controlled manner.

Various physicochemical properties of drug are required for the formulation of topical hydrogels such as;

1. Drug should have a molecular mass of <500 Daltons
2. Drug must have sufficient hydrophilicity.
3. Drug should have a pH range between 5.5 and 9.5.
4. Highly acidic or alkaline drugs are not appropriate for topical formulations.[43]

Classification

There are a variety of ways to classify hydrogels.

1.	**On the basis of the nature of the cross linked junctions [44]:**
a	Chemically cross-linked networks having permanent junctions.
b.	Physical networks have passing connection begins from polymer chain network or physical interactions namely, ionic interactions, hydrogen bonds or hydrophobic interactions.
2.	**On basis of the nature of the side groups/charge:**
a.	Neutral Hydrogels
b.	Ionic Hydrogels (Anionic and Cationic)
c.	Ampholytic Hydrogels
d.	Zwitterions Hydrogels
3.	**On basis of the source:**
a.	Natural Hydrogels
b.	Hybrid Hydrogels
c.	Synthetic Hydrogels
4.	**On the basis of structure:**
a.	Amorphous Hydrogels
b.	Semi-crystalline Hydrogels
c.	Crystalline Hydrogels
d.	Hydrogen bonded Hydrogels
5.	**On the basis of method of preparation:**
a.	Homo-polymer Hydrogels
b.	Co-polymer Hydrogels
c.	Multi-polymer Hydrogels
6.	**On the basis of mechanical and structural character:**
a.	Affine network
b.	Phantom network
7.	**On the basis of responsiveness to stimuli:**
a.	pH
b.	Ionic strength
c.	Temperature
d.	Electromagnetic radiation

Table 1: On the basis of origin.[45]

Characteristics	Natural origin	Synthetic Origin
Preparation	By using natural polymer	By chemical Polymerization
Advantages	Biocompatible Biodegradable Supports cellular activities	Absence of natural bioactive properties.
Disadvantages	Inadequate mechanical properties Presence of pathogen/microorganism Stimulate immune and inflammatory responses	----------
Examples	Proteins like collagen and gelatin. Polysaccharide like alginate and agarose	Acrylic acid, Vinyl acetate, Hydroxyethyl Methacrylate Methacrylic acid (MAA)

Table 2: List of Natural and synthetic polymer.

Natural polymer	Synthetic polymer
Shellac	Acrylic acid
Gelatin	Polyvinyl chloride
Silk	Polystyrene
Cellulose	Nylon (Polyamide)
Dextran	Teflon (Poly tetra fluoro ethylene)
Alginate	Polyvinyl Alcohol
Guar gum	Methacrylic Acid
Hyaluronic acid	Poly (N-vinyl pyrrolidone) PVV
Chitosan	Polypropylene

Table 3: Structure and release mechanism of Hydrogel in topical drug delivery.

Structure	Range	Release mechanism
Macro-porous	0.1-10µm	Depends on drug diffusion coefficient
Micro-porous	100-1000µm	Molecular diffusion and convection
Non-porous	10-100µm	Diffusion

Fig. 2: Images of hydrogels.

Advantages

1. It has an extent of elasticity like natural tissue, due to their considerable amount of water content.
2. In comparison to other drug delivery systems it shows sustained and prolonged action of drug.
3. Reduced frequency of dosing.
4. Hydrogel beads have a benefit of little side effects due to entrapment of the microbial cells.
5. Better drug utilization.
6. Improved patient compliance and reduced side-effects.
7. Targeting of drug to exact site like colon.
8. Protection of mucosa from irritating drugs.
9. Drug loss is restricted by first pass metabolism.
10. Reduced cost to patient due to decrease in the number of therapy which are essential to the patient.
11. Have good transport properties.
12. Biocompatible and injectable.
13. Easy to modify.
14. Hydrogels have the capability to sense alteration of pH, heat or the absorption of metabolite.
15. Natural hydrogel materials are considered for tissue engineering, which consist of agarose, methylcellulose, hylaronan, and other naturally obtained polymers.

Disadvantages

1. Cost is very high.
2. Low mechanical strength.
3. Difficult to load.
4. Difficult to sterilize.
5. Non-adherent.
6. In contact lenses - lens deposition, hypoxia, dehydration and red eye reactions.

Table 4: Marketed Products of Hydrogels.

S. No.	Name of Product	Uses
1.	Hydromer	Anti-thrombic DNA immobilization
2.	Aquamere (Coating hydrogel)	Cosmetics
3.	Dermaseal	Allergen blocker
4.	Aquatrix	Super absorbent
5.	Aquatrix II	Wound, Burn, Adhesive
6.	Medicell	Medicated foam for burns

Techniques Used For the Preparation Hydrogels

Various techniques for the preparation of hydrogel were used. These alterations are able to get better the physicochemical properties for the use in biomedical and pharmaceutical fields. Some of these techniques are discussed below.

1) Physical cross-linking
2) Chemical cross-linking
3) Grafting polymerization

1) Physical cross-linking: There has been an improved importance in physical hydrogels due to ease of making. These cross linkers influence the integrity of material to be entrapped (e.g. cell, proteins, etc.) as well as the need for their removal before application. The various methods reported in this article to achieve physically cross-linked hydrogels are:

A. Cross-linking by crystallization
B. Charge/Ionic interaction
C. Hydrogen bonding interaction
D. Hydrophobic interaction
E. Stereo complexation interaction

A. Cross-linking by crystallization (Heating/cooling a polymer solution): It involves freezing-thawing process and creates a physically powerful elastic gel. Formation of gel is due to development of helix and connection of the helices. To form hydrogel, Cross-linking of a polymer done by means of freeze-thaw cycles. Development of microcrystal in the polymeric structure is due to freeze-thawing cycle.

For examples: Polyvinyl alcohol (PVA) hydrogels are prepared by physically cross-linking through repeated freezing/thawing methods or chemically cross linked with glutaraldehyde or epichlorohydrin. PVA is a water soluble polymer. Aqueous solution of PVA stored at room temperature, progressively it form a semi-solid solution with a poor mechanical strength. When solution of this polymer passes through the freeze-thawing process, it produces a strong elastic gel. The characteristics of hydrogel based on the molecular mass of polymer, amount of water, temperature and time of crystallization and number of freezing cycles. Gel formation is accredited to the arrangement of PVA crystals which works as physical cross-linking sites in the network. Gels produced under optimized condition for 6 months at 37^0. The gel characteristics based on the polymer concentration present in solution. Some of the examples are polyethylene oxide, polypropylene oxide, polyethylene glycolpolylactic acid hydrogel etc.

B. Charge/Ionic interaction: Cross-linking of polymer by the addition of di- or tri-valent ions. Metallic ions produce stronger hydrogel. This method depends on the hypothesis of gelling polyelectrolyte solution (e.g. Na^+ $alginate^-$) with a multi-valent ion of opposite charges (e.g. $Ca2^+ + 2Cl^-$).

For example: Alginate a natural polysaccharide having mannuronic and gluccuronic acid remains and calcium ions ($Ca2^+$) cross-linking. It can be prepared at room temperature and physiological pH. As a result, alginate gels are formed as medium for the entrapment of living cells and protein for release. The liberation of proteins from alginate, done by spraying sodium alginate solution into an aqueous solution of calcium chloride, can be altered by coating the cationic polymer particles.

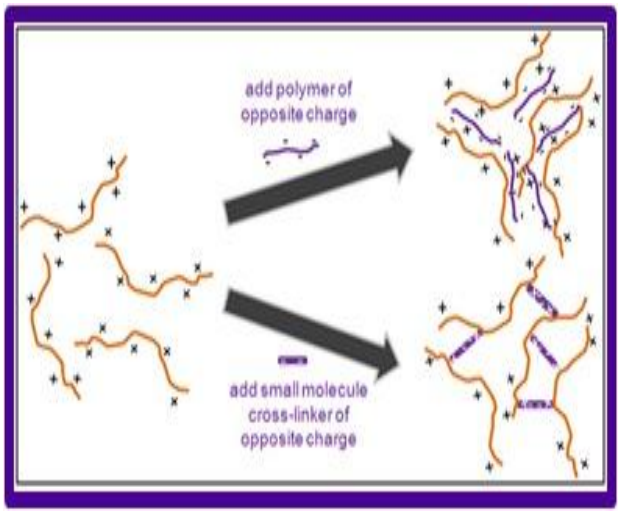

Fig. 3: Mechanisms of oppositely-charged polymer cross-linker based on charge interactions.

C. Hydrogen bonding interaction: H-bonding between polymers can also take part in hydrogel preparation e.g. development of gelatin based hydrogel. In this method the hydrogen bond is produced by the participation of an electron deficient H-atom and a functional group with high electro-negativity. Hydrogels extended by this method are subjected by a number of factors like polymer concentration, molar ratio of polymer, type of solvent, solution temperature, and degree of association of polymer.

For example: Complexation of Polyacrylic acid and polymethacrylic acid with PEG. These complexes have hydrogen-bonding between the oxygen of the polyethylene glycol and the carboxylic group of polyacrylic acid and polymethacrylic acid. Hydrogen bonds are produced by the protonation of carboxylic acid groups which shows pH dependent growth of the gels.

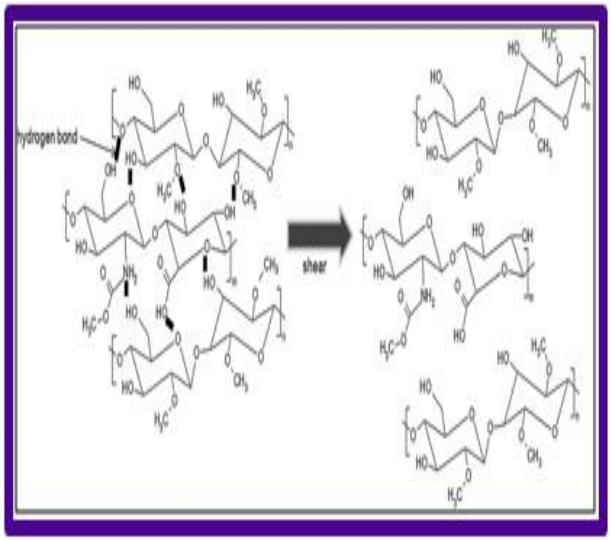

Fig. 4: Hydrogen bonding interactions between polyacrylic acid/polymethacrylic acid and polyethylene glycol.

D. Hydrophobic interactions: Hydrophobic interaction done by cross-linking of polymer in aqueous medium by means of reverse thermal gelation, also called as 'solegel'. Polymers with such properties are known as gelators and they are hydrophobic in nature.

For example, a hydrophobic part is attached to a hydrophilic polymer part by producing a copolymer to generate a polymer amphiphile. At low temperature amphiphiles are water soluble. As the temperature rises hydrophobic domains are connected with hydrophilic domain to form a gel. Gelation of medium depends on the amount of the polymer, chemical structure of the polymer, length of the hydrophobic segments.

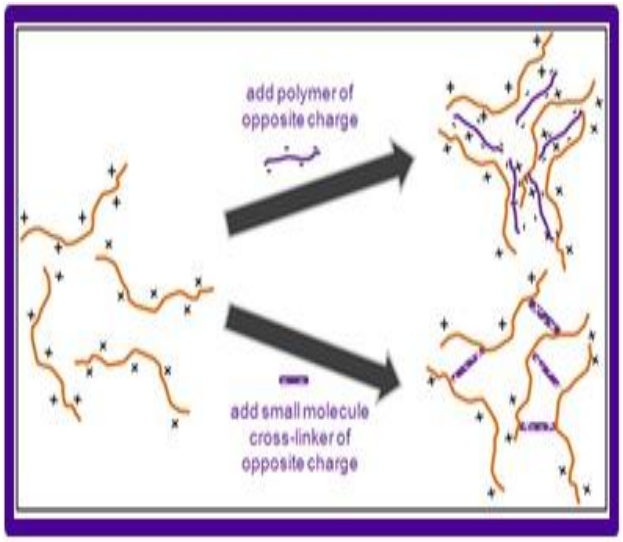

Fig. 5: Mechanism of in situ physical gelation driven by hydrophobic interactions.

E. Stereocomplexation interaction: Stereo complexation interactions occur between polymer chains or small molecules of the same chemical composition but different stereochemistry. Hydrogels are prepared by the strong interaction between polylactide blocks with L- and D stereochemistry. Interaction of L-lactide and D-lactide oligomers to dextran precursors stimulates gelation in water and produces an outstanding biocompatible and biodegradable gel without requiring the organic solvents and chemical cross-linkers.

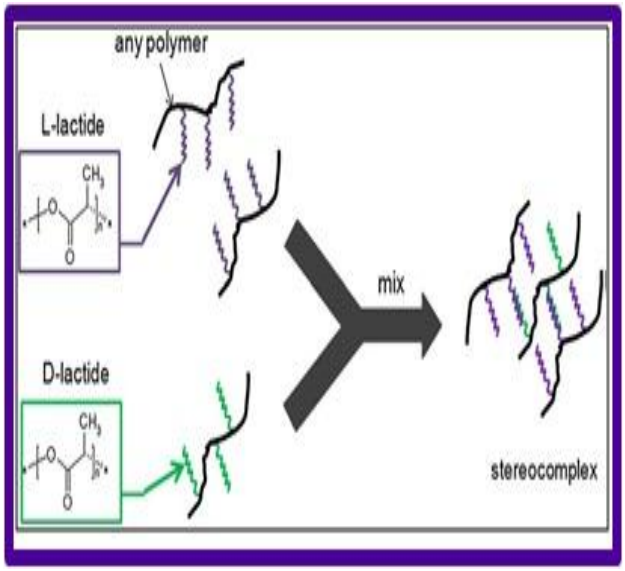

Fig. 6: Mechanism of L- and D- lactide polymer chains by stereocomplexation interaction.

2. Chemically cross-linked hydrogels: Now-a-day importance of chemically cross-linked hydrogels is increased due to the excellent mechanical strength of chemically cross-linked hydrogels.

There are the following methods to produce chemically cross-linked hydrogels.

A. Cross-linking with aldehydes: Polymers having hydroxyl groups e.g. polyvinyl alcohol could be cross-linked via glutaraldehyde. To create cross-linking, various predetermined physicochemical conditions are applied like pH, methanol as a quencher, high temperature. On the other hand, polymers with amine-groups may be cross-linked by apply the equivalent cross-linker under mild conditions in which Schiff bases are produced. It was particularly planned for the protein synthesis.

B. By addition reactions: Through addition reactions, cross-linkers may be used to react with functional groups of hydrophilic polymers. When monomers bonds are joined together without losing any atom, addition reaction happened. Polysaccharides may be cross-linked with 1,6 hexamethylene di-isocyanate, di-vinylsulfone, or 1,6-hexanedibromide.

C. By condensation reactions: Polyesters and polyamides can be prepared by condensation reactions with the –OH groups or –NH2 with –COOH correspondingly. Condensation reactions are used for the synthesis of hydrogel. An extremely competent reagent for cross-linking hydrophilic polymers having amide groups is N, N-(3-dimethylaminopropyl)-N-ethyl carbodiimide (EDC). Hydrogel was designed as a tool for antibacterial proteins release and was loaded into a prosthetic valve of Dacron.

D. Cross-linking by high energy radiation: Ionoizing-radiation method is very precious technique for the production of hydrogels. Gama rays, X- rays and electronic beam are used for polymerization.
For example: By using high energy radiation, water soluble polymers integrated with vinyl groups which are changed into hydrogels.

E. Cross-linking by free radical polymerization: This is the ideal method of preparing hydrogels based on a number of monomers such acrylates, amides, and vinyl lacyams. Chemically cross-linked hydrogels may be produced by free radical polymerization of polymerizable group derivatized hydrophilic polymers. Natural, synthetic and semi-synthetic hydrophilic polymers were used for the hydrogel synthesis in the presence of enzymes as catalyst.

F. Cross-linking using enzymes: A new and smart way of preparing hydrogel was planned to produce PEG-based gels by using an enzyme.

For example: Tetrahydroxy PEG (PEG-Qa) was obtained by adding glutaminyl groups. Development of PEG networks by adding transglutaminase into aqueous medium of poly (lysine-cophenylalanine) and tetrahydroxy PEG. Transglutaminase accelerate reaction among the γ-carboxamide group of the tetrahtdroxy PEG and the e-amine group of lysine consequence in the formation of an amide bond.

3. Grafting polymerization: To improve the mechanical properties of a hydrogel, the polymerization of a monomer with polymer involved. The polymer chains are triggered by the activity of chemical or high energy radiation action.

For example: Starch mixed with acrylic acid by using N-vinyl-2-pyrrolidone. This type of hydrogels shows an outstanding pH-dependent swelling behaviour and has ultimate quality to be used as drug and vitamin carrier in targeted organ.

Characterization of Hydrogels

Hydrogels are differentiating for their morphology, swelling ability and elasticity. Various methods for characterization of hydrogels are as follows:

1. Morphological Characterization: Hydrogels are distinguished for morphology which is investigated by tool like SEM (Scanning Electron Microscopy). This equipment is able to give detailed data about the sample's surface arrangement, composition, and electrical conductivity. In SEM magnification can be range from about 10 to 500,000 times. It is a powerful method mostly used to confine the feature 'network' structure in hydrogels.

2. Swelling property: It determines the drug release from swollen polymeric network. The hydrogels are allowed to dip in liquid medium to identify the swelling ability of polymeric chains. The absorbed liquid acts as a filter to permit free distribution of solute molecules, at the same time as the polymer acts as a matrix to keep the liquid together. Hydrogels may soak up from 10-30% up to thousands of times of their dry weight in water. Swelling degree of hydrogels was measured at 37^0. The freshly prepared samples were weighed and dipped in buffer solution with different pH. The samples were remove from the solution and gently clean with filter paper to remove excess amount of solution from surface of hydrogel, then weighed and returned to the same container at pre-determined time intervals.

$$\textbf{SD \% = (Wt/Wo) x 100}$$

Where,
Wo = weight of the original hydrogel.
Wt = weight of the hydrogel at various swelling times.

3. Elasticity: It determines the stability and mechanical strength of drug carrier and polymeric structure.

4. Viscosity: Viscosity of hydrogels is calculated under constant temperature of usually 4℃ by using viscometer like Cone Plate type. This is highly specific and accurate equipment for the evaluation of viscosity. Solution of Polymers is viscous at low frequencies. At high frequencies, elasticity obtained.

5. X-ray diffraction: It is used to identify crystalline structure of the polymers. X-ray diffraction is mainly used for the estimation of impurities in powder that find out the arrangement pattern of the hydrogel layers which are scattered.

6. *In-Vitro* Diffraction: The *in-vitro* diffraction method is quite popular for studying the release profile of hydrogel. To calculate the release of drug from dosage forms bioequivalence study is carried out. The parameters are synchronized with the data of the reference drug so that the similarity between the drug solutions is done.

7. *In-vitro* release study for drugs: To understand the polymeric networks, inner structure of drug molecules, mechanism of drug release over a period of time, in-vitro release studies are carried out.

8. FTIR (Fourier Transform Infrared Spectroscopy): FTIR is a method for identifying chemical structure of a material. FTIR spectroscopy technique is based on studying the contact of infrared radiation with samples. This method is broadly used to explore the polymeric network arrangement in hydrogel.

Application of hydrogels

- **Wound Healing:** Cartilage present in the modified polysaccharide is used in hydrogels to treat cartilage defects. For example, combination of gelatin and polyvinyl alcohol (PVA) are used as blood coagulants.
- **Soft Contact Lenses**: The first silicon hydrogels available in the market assume two different approaches. First approach by Bausch and Lomb was a logical extension of its development of silicon monomers with enhanced compatibility in hydrogel forming monomers. The second by Ciba vision was the development of siloxy monomers containing hydrophilic polyethylene oxide segments and oxygen permeable polysiloxane units.
- **Industrial Applicability:** Hydrogels are used as absorbents for industrial waste matter like methylene blue dye. Another example is adsorption of dioxins by hydrogel beads.
- **Tissue Engineering:** In this field hydrogel play an important role. They are used as a carrier or transporter of macromolecules (phagosomes) into cytoplasm of antigen-presenting cells.
- **Drug Delivery in GI Tract:** Hydrogel distribute drugs to targeted sites in the GIT. Drugs loaded with colon specific hydrogels show tissue specificity and change in the pH or enzymatic actions cause liberation of drugs.
- **Rectal Delivery:** Hydrogels exhibit bioadhesive properties are used for rectal drug delivery. Miyazaki et al. explored the xyloglucan gel with a thermal gelling property as matrices for drug delivery.
- **Ocular Delivery** Chitoni et al. reported silicon rubber hydrogel complex ophthalmic inserts. Cohen et al. Developed ***in-situ*** forming gelling system of alginate with high gluconic acid contents for the ophthalmic delivery of pilocarpine.
- **Transdermal Delivery:** Swollen hydrogels can be used as controlled release devices in the field of wound dressing. Hydrogel based formulations are being explored for transdermal iontophoresis to obtain enhanced permeation of products viz. hormones and nicotine.
- **Subcutaneous Delivery:** Hydrogel formulations for subcutaneous delivery of anticancer drugs are being prepared viz. cross-linked PHEMA was applied to cytarabine (Ara-c). Implantable hydrogels are now leading towards the development of biodegradable systems which don't require surgical removal once the drug has been administered.[46,47]
- **Novel Hydrogel for Controlled Drug Delivery:** HYPAN is the novel hydrogel having properties useful controlled drug delivery system. Physical network of crystalline clusters distinguishes HYPAN hydrogels from others.[48,49]
- **Hydrogel for Gene Delivery:** Modification of hydrogel composition leads to effective targeting and delivery of nucleic acids to specific cells for gene therapy. Hydrogel versatility has potential application in the treatment of many genetic disorders and/or acquired diseases and conditions.
- **Cosmetology:** Hydrogels when implanted into breast accentuate them for aesthetic reasons. These implants have silicon elastomer shell and are filled with hydroxyl propyl cellulose polysaccharide gel.
- **Tropical Drug Delivery:** Instead of conventional creams, hydrogel formulations are employed to deliver active components like Desonide, a synthetic corticosteroid used as an anti – inflammatory for better patient compliance.
- **Protein Drug Delivery:** Interleukins conventionally administered as injection are now given as hydrogels which show better compliance and form *in-situ* polymeric network and release proteins slowly.
- **Perfume delivery:** The role of hydrogels in the process revolves around, once again, their swelling properties that can be exploited inmaterials "wherein release of a perfume smell is triggered by dynamic swelling force of the polymer when the polymer is wetted". These devices release volatile particles thanks to osmotic diffusion of the specie from the swollen hydrogel to new water in the environment.
- **Dental applications:** Pulp regeneration therapy is important to overcome the limitations of conventional therapy to induce reparative dentinogenesis. Fibroblast growth factor-2 (FGF-2), which is normally stored in the extracellular matrix and released by enzymatic degradation of extracellular matrix molecules, plays a role in physiologic conditions such as enamel and dentin formation of the tooth germ , as well as pathologic conditions . It was previously demonstrated that a

gradual and continual release of biologically active FGF-2 was achieved by *in-vivo* biodegradation of gelatin hydrogels that incorporated FGF-2. Furthermore, a controlled release of FGF-2 from gelatin hydrogels induced neovascularization and regeneration of several tissues, including bone, periodontal tissues.[50]

CONCLUSION

Hydrogels are three dimensional (3D), cross-linked polymer structures that absorb extensive amount of water. Presence of huge amount of water, these hydrogel looks like natural living tissue. Hydrogels have an exclusive combination of characteristics that make them useful in drug delivery application. Hydrogel can absorb huge amount of water due to its hydrophilic nature. As an alternative of conventional creams, the hydrogels have been developed for improved patient compliance. Hydrogels played a significant role in biomedical and pharmaceutical applications. Hydrogels have played a significant role in biomedical applications. Significant progress has been made in improving the properties of hydrogels used for drug delivery and expanding the range of drugs and kinetics which can be achieved using a hydrogel based delivery vehicle. Reduced release efficiency, burst effects, complex geometries and unknown correlation between *in vitro* and *in vivo* release complicates our understanding of these devices. This review provides adequate information of hydrogel in drug delivery to the targeting site and their application in various fields. These hydrogels are biocompatible and biodegradable in nature that is why used for various novel drug deliveries. There is need for continued improvement in the delivery of not only hydrophobic molecules, but also the delivery of more sensitive molecules viz. proteins, antibodies or nucleic acids which gets deactivated by interactions with the hydrogel delivery vehicle. Solution of such problems would greatly expand the potential of hydrogel based drug delivery to successfully deliver the next generation drugs at the desired rate and location in the body.

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