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REVIEW ON HYDROGEL AS A NOVEL CARRIER

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Abstract

Hydrogel product constitute a group of polymeric material, the hydrophilic structure of which render them capable of holding large amount of water in their three dimensional networks. Due to their high water content, porosity and soft consistency, they closely simulate natural living tissue, more so than any other class of synthetic biomaterials. Several techniques have been reported for synthesis of hydrogel like co-polymerization/crosslinking of co-monomers using multifunctional co-monomers, which acts as crosslinking agent. They can be classified in different ways on the basis of their preparation, biodegradable properties, polymer sensitivity to surrounding environment and also their applications.
Synthetic hydrogels offer a possibly effective and convenient way to administer these compounds.
Hydrogels can be used as biosensors as well as drug delivery systems that are responsive to specific molecules, such as glucose or antigens. In this review article an attempt has been made to describe the available methods of hydrogel synthesis, classification of hydrogels, their properties, method of preparation and its application.

Key words: Hydrogel, Chemical cross-linking, Polymer, Classification, Application.

INTRODUCTION

Hydrogels are hydrophilic, three dimensional network that hold the large quantity fluid water is the large constituents of human body which applied for the biomedical purposes. [1] and first proposed by Witchterle and Lim in the 1960s. Hydrogels are generally cross-linked by physical or chemical methods which have been widely used for drug release, cell culture, tissue engineering and adhesion.
Polymers used in hydrogel can be divided into natural polymer hydrogels and synthetic polymer hydrogels. Synthetic polymers are formed by chemical reactions of small organic monomers. Synthetic polymers possess strong water absorption and excellent mechanical properties, a certain extent of biodegradability and potential toxicity have limit the application of polymer hydrogel. As a natural ingredient, protein has different genetic coding structures and functions with biocompatibility and degradability. [2] Hydrogels formulation applied on the skin surfaces which categories into two groups such as topical and transdermal route. Topical formulations provide the drug at the particular site of the skin surfaces without systemic exhibition while transdermal

formulations applied to the local area of the skin surfaces which maintain and deliver the effective concentration of drug in the systemic circulations. [1]

ADVANTAGES [3]

1. Hydrogel is more elastic and stronger.
2. Due to their significant water content they possess a degree of flexibility very similar to natural tissue.
3. Hydrogel possess good transparent properties and easy to modification.
4. They are biocompatible, biodegradable and can be injected.
5. Release of Medicines or nutrients timely.
6. Hydrogel have ability to sense change pH, temperature, or the concentration of metabolite and release their load as result of such a change.
7. They can be injected.
8. More resistance to protein deposits.
9. Soothing effect promotes patient acceptance.

DISADVANTAGES [3,4]

1. High cost.
2. Low mechanical strength
3. Difficult to sterilize
4. In contact lens less deposition hypoxia, dehydration and red eye reactions.
5. Non-adherent

APPLICATIONS OF HYDROGEL [5]

Hydrogels have a very wide application different area but most importantly, these materials find their importance in biomedical and bioengineering. Medical textiles, which are the basic core of the medicine, can be delivered in most cases by using these hydrogels. Though medicine and health care do need a lot of cautions like biocompatibility, biodegradability, and other factors, still hydrogels, which are natural polymer based especially gelatin-based ones, have a lot of significance.

1. **Wound Dressing -** Modern dressings are designed to facilitate wound healing rather than just to cover it. Specific properties of hydrogels such as high surface area, absorbency phenomenon, and variety in product forms are advantageous properties of hydrogels, which makes using them in wound dressing applications desirable.

2. **Contact Lenses -** Wichterle and Lim were the first to describe a hydrogel as a synthetic biocompatible material useful for contact lens applications which were based on poly-2-hydroxyethyl methacrylate (PHEMA) in 1960, most important advances made on the aspects of contact lenses are the development of silicone-based hydrogels. These provide the property of higher oxygen permeability which protects contact lens wearers especially those who apply them in the night from “induced hypoxia on corneal physiology.

3. **Drug Delivery Vehicles** - Over the past decades, natural polymers (biopolymers) have frequently been used as raw materials for the design of efficient drug delivery systems. Among the different drug delivery systems, hydrogels have particular properties that let them be used as ideal drug delivery systems which is the fact that they are similar to the body's tissues; they have high water content and rubbery consistency. Carrageenan and gelatin-based hydrogels were prepared to apply as a topical drug delivery system. The developed gels were found to be smooth in texture, stable, and hemocompatible in nature. The drug-loaded gels showed sufficient antimicrobial efficacy to be used as a topical antimicrobial gel.

4. **Tissue Engineering** - Hydrogels are insoluble hydrophilic polymer networks that are imparted with tissue-like mechanical property and high water content and to make them highly compatible for scaffolds for implantation in empty tubular nerve prosthesis or for direct injection at the lesion site to enhance cell attachment and growth

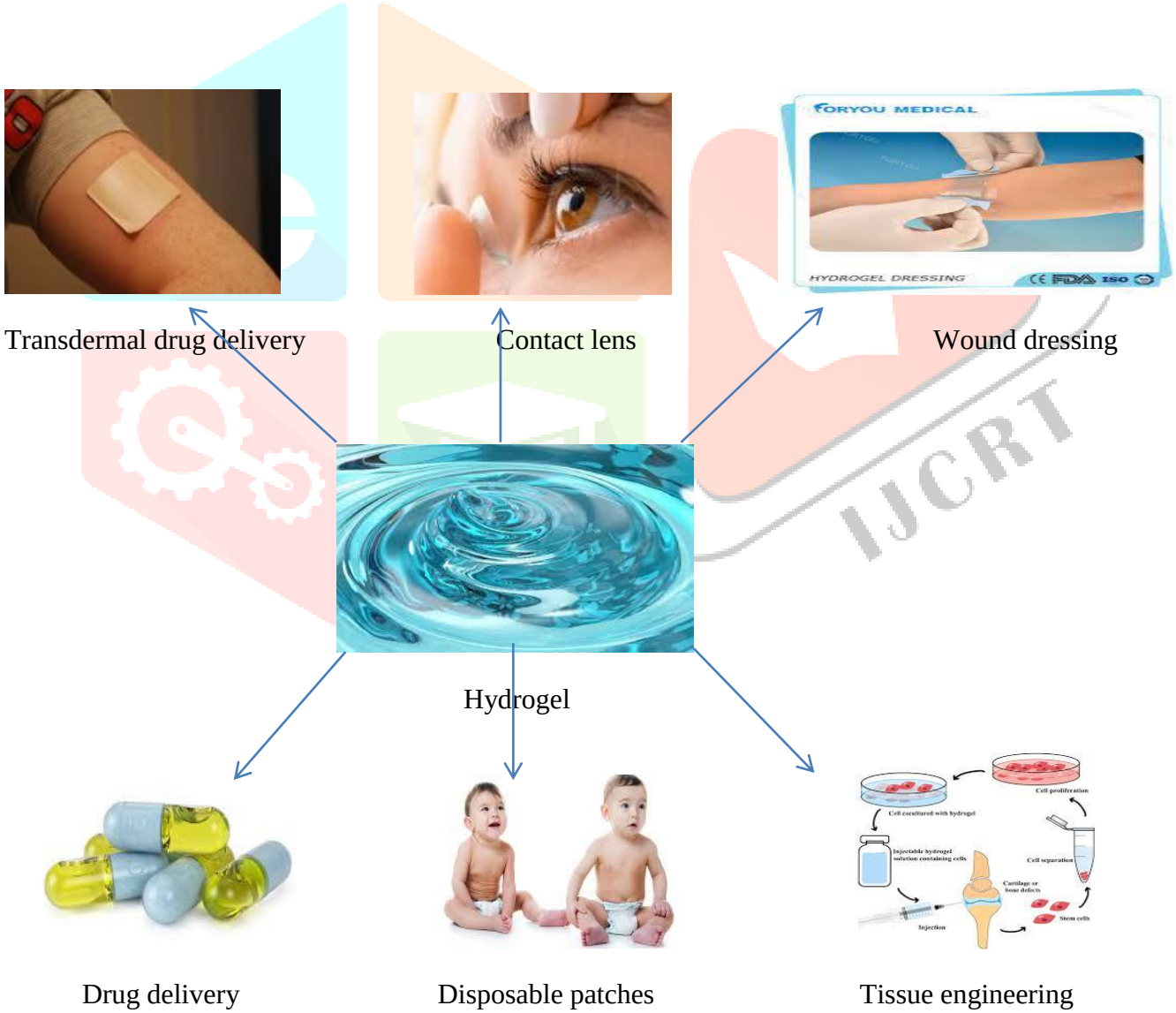


Figure no.-1 Application of hydrogels in various industries.

DESIRED FEATURES OF HYDROGEL MATERIAL [6]

The functional features of an ideal hydrogel material can be listed as follows

1. Must have highest absorption capacity (maximum equilibrium swelling) in saline.
2. Must show desired rate of absorption (preferred particle size and porosity) depending on the application requirement.
3. Must exhibit the highest absorbency under load (AUL).
4. Should show lowest soluble content and residual monomer.
5. Have lowest price.
6. Must have highest durability and stability in the swelling environment and during the storage.
7. Must have highest biodegradability without formation of toxic species following the degradation.
8. pH-neutrality after swelling in water.
9. Colorless, odorless, and absolutely non-toxic.
10. Must have good photo stability.
11. Re-wetting capability (if required) the hydrogel has to be able to give back the imbibed

CLASSIFICATION OF HYDROGEL [7]

The hydrogel products can be categorized on different bases as described below:

A. Classification based on source

Hydrogel can be classified into two origins.

Natural origins

Natural polymers occur in nature and can be extracted. They are often water-based.
E.g.: Natural origins; silk, wool, DNA, cellulose and proteins.

Synthetic polymers

Include nylone, polyethylene, polyester, Teflon and epoxy.

B. Classification according to polymeric composition

I) Homopolymeric hydrogels

These are referred to polymer network which are derived from a single species of monomer, which is the basic structural unit comprising of any polymer network. Homo polymers may have cross-linked skeletal structure dependent on the nature of the monomer and polymerization.
Cross linked homo-polymers are used in drug delivery system and in contact lenses.
eg; nylon6, nylon11, polyethylene, polypropylene.

II) Copolymeric hydrogels

These are consisted of two or more distinct monomer species with at least one hydrophilic component, assembled in a random, block or alternating configuration along the chain of the polymer network.
eg; Acrylonitrile butadiene styrene, styrene –isoprene-styrene.

III) Multi-polymer

These are also called as interpenetrating polymeric hydrogel (IPN). An important class of hydrogels, which is made of two independent cross-linked synthetic and / or natural polymer component, confined in a network form. In semi-IPN hydrogel, one component is a cross-linked polymer and other component is a non-cross-linked polymer.

C) Classification based on configuration

These classification of hydrogels relies on their physical structure and chemical composition which can be illustrated as follows

• Amorphous (non- crystalline)

• Semi crystalline (A complex mixture of amorphous and crystalline phase.)

• Crystalline.

D. Classification based on type of cross-linking

Hydrogel can be divided into two groups on the basis of cross-link junctions. Chemically cross-linked networks have stable junctions, while physical network have temporary junctions that results from either polymer chain entanglements or physical interactions, hydrogen bonds or hydrophobic interactions.

E. Classification based on physical apperance

Hydrogels appearance as matrix, film or microsphere is dependent on the procedure of polymerization employed in the formulation process. Hydrogels may be classified into four groups on the basis of presence or absence of electrical charges situated on the cross-linked chains.

1. Nonionic (neutral)

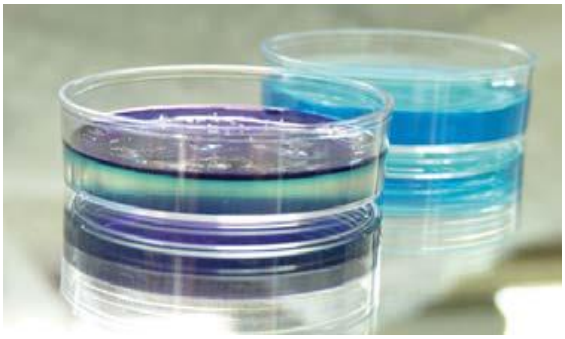
2. Ionic (including anionic or cationic)

3. Amphoteric electrolyte (ampholytic) comprising both acidic and basic groups.

4. Zwitter ionic (poly betaines) consisting of both anionic and cationic groups in each structural repeating unit.

Figure no.-2 Nano hydrogel that attack cancer cell Silicon hydrogel contact lens

Self healing hydrogel



Synthetic hydrogel [8]

TECHNOLOGIES ADOPTED IN HYDROGEL PREPARATION [9]

Hydrogels are polymer networks having hydrophilic properties. Hydrophilic monomers, hydrophobic monomers are sometimes used in hydrogel preparation to regulate the properties for specific applications. Hydrogels can be produced by reacting hydrophilic monomers with multifunctional cross-linkers by using Copolymerization/ cross-linking free-radical polymerizations. Water-soluble linear polymers of both natural and synthetic origin are cross- linked to form hydrogels in a number of ways:

1. Using ionizing radiation to generate main-chain free radicals which can recombine as cross-link junctions.
2. Linking polymer chain via chemical reaction.
3. Physical interaction such as entanglements, electrostatics and crystalline formation.

In general, the three integral parts of the hydrogels preparation are monomer, initiator, and cross-linker.

A. Bulk polymerization

Bulk hydrogels can be formed with one or more types of monomers mainly include vinyl monomers for the productions of hydrogels. Usually, a small amount of cross- linking agent is added in any hydrogel formulation. Radiation, ultraviolet, or chemical catalysts is used for the initiation of the polymerization reaction. The initiator is chosen which depends upon the type of monomers and solvents being used. The polymerized hydrogel may be produced in a wide variety of forms including rods, particles, films and membranes, and emulsions.

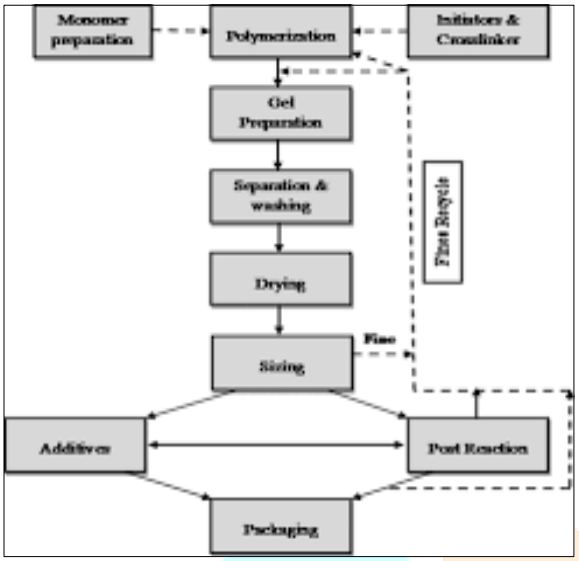
B. Free radical polymerization

The main monomers which are used in this method for the preparation of hydrogels are such as acrylates, vinyl lactams and amides. These polymers have suitable functional groups or have been functionalized with radically polymerizable groups. This method involves the chemistry of typical free-radical polymerizations, which includes propagation, chaintransfer, initiation, and termination steps. For the radical generation in the initiation step a wide variety of thermal, ultraviolet, visible, and redox initiators can be utilized, the radicals react with the monomers which convert them into active forms.

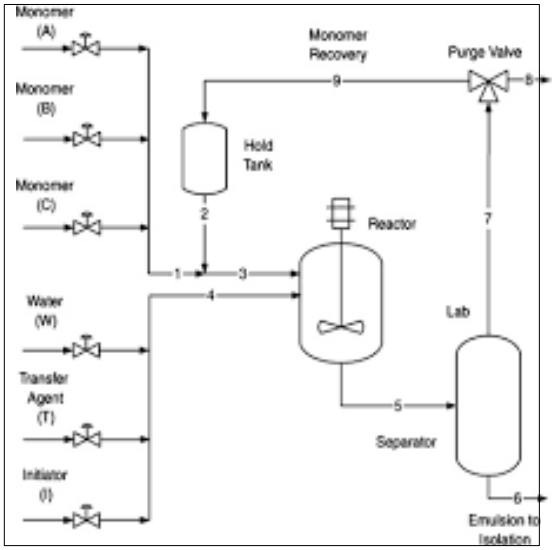
C. Solution polymerization/cross-linking

In these ionic or neutral monomers are mixed with the multifunctional crosslinking agent. The polymerization is initiated thermally by UV-irradiation or by a redox initiator system. The major advantage of the solution polymerization over the bulk polymerization is the presence of solvent serving as a heat sink. The prepared hydrogels is washed with distilled water to remove the initiator, the soluble

monomers, oligomers, cross-linking agent, and extractable polymer, and other impurities. Solvents used water–ethanol mixtures, water, ethanol, and benzyl alcohol.



A

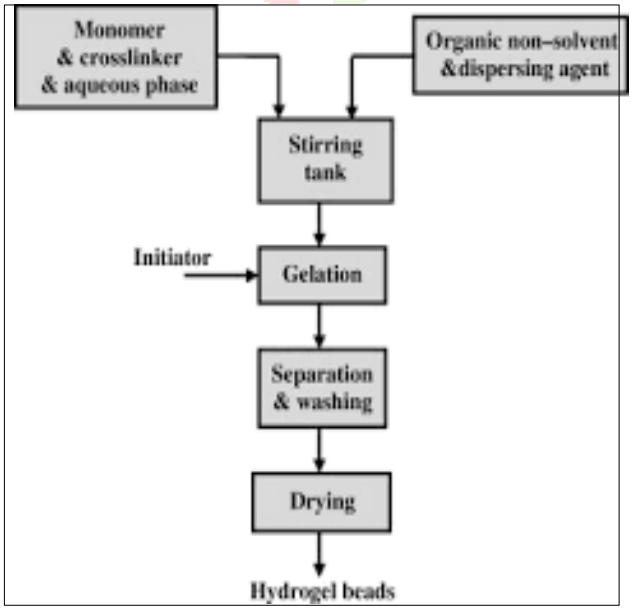


B

Figure no.-3 A. Hydrogel preparation block diagram B. solution polymerization with recycle loop

D. **Suspension polymerization or inverse-suspension polymerization**

The advantageous of this method is that the products obtained as powder or microspheres (beads), and thus, grinding is not required. Since water-in-oil (W/O) process is chosen instead of the more common oil-in-water (O/W), the polymerization is referred to as ‘‘inverse suspension’’. In this technique, the monomers and initiator are dispersed in the hydrocarbon phase as a homogenous mixture. The resin particle size and shape is used to govern the viscosity of the monomer solution, rotor design, agitation speed, and dispersant type. The dispersion is thermodynamically unstable and requires both continuous agitation and addition of a low hydrophilic–lipophilic- balance (HLB) suspending agent.



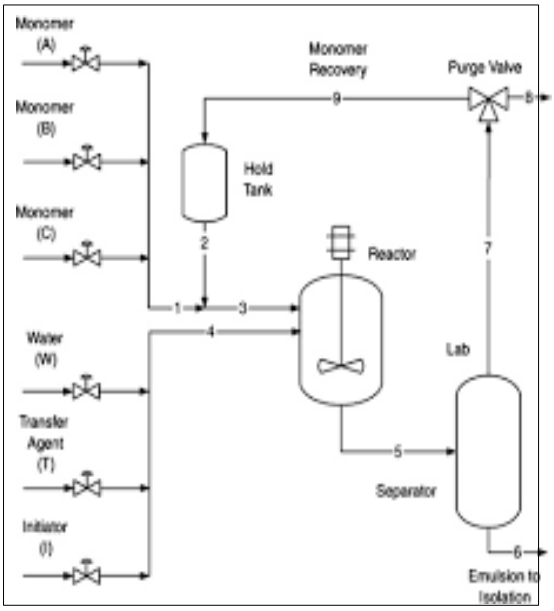


Figure no.-4 Suspension polymerization with recycle loop

E. Grafting to a support

Due to the weak structure of hydrogels prepared by bulk polymerization it is necessary to improve the mechanical properties of a hydrogel, so it can be grafted on surface coated onto a stronger support. This involves the generation of free radicals onto a stronger support surface and then polymerizing monomers directly onto it to form chain of monomers which are covalently bonded to the support.

F. Polymerization by irradiation

For the preparation of hydrogels of unsaturated compounds the initiators such as the ionizing high energy radiation, like gamma rays and electron beams, has been used. The irradiation of aqueous polymer solution results in the formation of radicals on the polymer chains. Recombination of the macro-radicals on different chains results in the formation of covalent bonds, so finally, a cross-linked structure is formed. Poly (vinyl alcohol), poly (ethylene glycol), and poly (acrylic acid) is used for polymerization by irradiation. Relatively pure and initiator-free hydrogels is produced by this method.

G. Physical cross-linking

It is the most common and easy routes for hydrogel formation by cross linking of polymers through physical interactions. This physical cross linking includes interaction of ions such as hydrogen bonding, polyelectrolyte complexation and hydrophobic association. The various methods used in physically cross-linked hydrogels preparation are:-

Heating/cooling a polymer solution - It is prepared by cooling hot solutions of gelatin or carrageenan to form physically cross-linked gels. The gel formation is due to association of the helices, helix-formation, and forming junction zones. Some of the examples are polyethylene glycol-polylactic acid hydrogel and polyethylene oxide-polypropylene oxide.

Complex coacervation - Formation of complex coacervate gels by mixing of polyanions with a polycations. The underlying principle of this method is that polymers with opposite charges stick together and form soluble and insoluble complexes depending on the concentration and pH of the respective solutions. One such example is coacervating polyanionic xanthan with polycationic chitosan.

Ionic interaction - Addition of di- or trivalent counter ions in ionic polymer leads to cross linking between polymers. This method underlies the principle of gelling polyelectrolyte solution (e.g. Na+ alginate-) with a multivalent ion of opposite charges (e.g. Ca2+ + 2Cl-). Some other examples are chitosan-polylysine, chitosan-glycerol phosphate salt, and chitosan dextran hydrogels.

Hydrogen Bonding- A hydrogen bond is formed through the association of electron deficient hydrogen atom and a functional group of high electron density. Example, a hydrogel can result from hydrogen bond formation between PA and PNVP. The factors which affect the hydrogels are the molar ratio of each which affect the hydrogels are the molar ratio of each polymer, polymer concentration, the type of solvent, the solution temperature, and the polymer structure.

Chemical cross-linking- In this process the use of a crosslinking agent to link two polymer chains and grafting of monomers on the backbone of the polymers takes place. The cross-linking of natural and synthetic polymers can be achieved through the reaction of their functional groups (such as OH, COOH, and NH2) with cross-

linkers such as aldehyde (e.g. glutaraldehyde, adipic acid dihydrazide). IPN is a polymerize monomer within another solid polymer to form interpenetrating network structure.s

DRUG RELEASE MECHANISM [10]

Diffusion controlled: Most common drug release mechanism for hydrogel is Diffusion controlled. Fick's law of diffusion with either constant or variable diffusion coefficients is commonly used in modeling diffusion controlled release. Drug diffusivities are generally determined empirically or estimated a prior using free volume, hydrodynamic, or obstruction-based theories.

Chemically controlled: Chemically-controlled release is used to describe molecule release determined by reactions occurring within a delivery matrix. The most common reactions that occur within hydrogel delivery systems are cleavage of polymer chains via hydrolytic or enzymatic degradation or reversible or irreversible reactions occurring between the polymer network and releasable drug. Under certain conditions the surface or bulk erosion of hydrogels will control the rate of drug release. Alternatively, if drug-binding moieties are incorporated in the hydrogels, the binding equilibrium may determine the drug release rate. Chemically-controlled release can be further categorized according to the type of chemical reaction occurring during drug release. Generally, the liberation of encapsulated or tethered drugs can occur through the degradation of pendant chains or during surface erosion or bulk-degradation of the polymer backbone.

Swelling controlled: Swelling-controlled release occurs when diffusion of drug is faster than hydrogel swelling. The modeling of this mechanism usually involves moving boundary conditions where molecules are released at the interface of rubbery and glassy phases of swollen hydrogels.

Drug diffusion from the core through the hydrogel membrane [11]

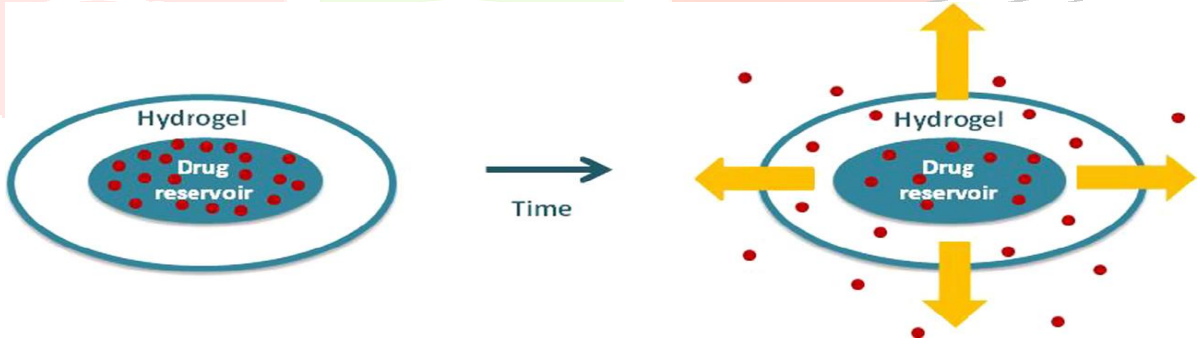


Figure no.-5 Scheme of drug release through a hydrogel membrane in a reservoir system.

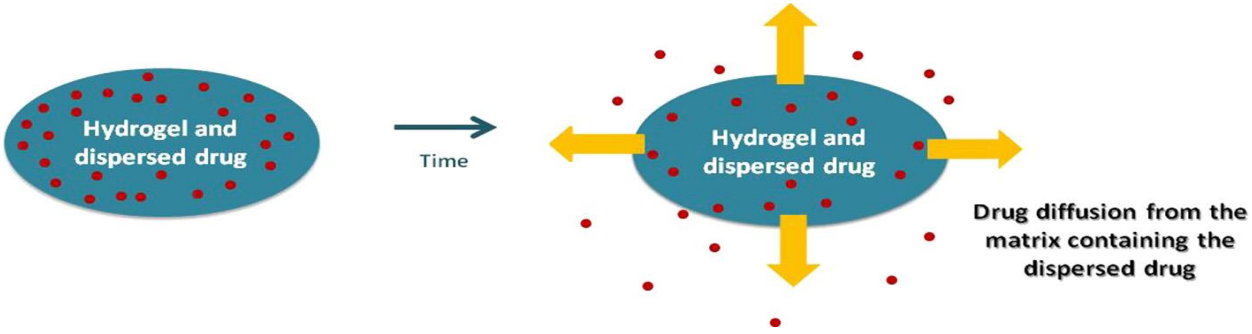


Figure no.-6 Drug release from matrix systems.

Table no-1 Hydrogel-based products on the market [12]

Product	Hydrogel composition	Indication	Product Manufactured by/Marketed by	Review	References
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
SQZ Gel oral release system	Chitosan and polyethylene glycol	Hypertension	Macromed (Sandy, UT, USA)	pH-Sensitive, once a-day tablet of Dilteazem Hydrochloride	http://www. macromed.com
Aquamere™	Interpolymers of PVPand PVPgrafted copolymers with urethane	Skincare, topical and oral drug delivery	Hydromer (Somerville, NJ, USA) Inte		http://www. hydromer.com
Hycore-V™ and Hycore-R™		Vaginal and rectal infections, respectively	(Irvine, UK) ™ CeNeS Drug Delivery	Localized delivery of Metronidazole	http://www. cenes.com
Smart C Hydrogel	Liquid Poly(acrylic acid) (oxypropylene-, co-oxyethylene) glycol.	Used for development 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

CHARACTERIZATION OF HYDROGELS [9]

1. **pH -** pH of hydrogels is measured by using digital pH meter. pH meter must be calibrated before its use.

2. **Scanning Electron Microscopy (SEM) -** SEM can be used to provide information about the sample's composition, surface topography, and other properties such as electrical conductivity. Magnification in SEM can be controlled over a range of up to 6 orders of magnitude from about 10 to 500,000 times.

3. **Fourier Transform Infrared Spectroscopy-** It is a useful technique for identifying chemical structure of a substance. It is based on the principle that the basic components of a substance, i.e. chemical bonds, can be excited and absorb infrared light at frequencies that are typical based on chemical bonds.

4. **Swelling measurement -** There are present three different methods by which we can measure swelling in hydrogels:-
   Method A- In this method the dry hydrogel is immersed in deionized water for 48 hours at room temperature on a roller mixer After swelling, the hydrogel is filtered by a stainless steel net of 30 meshes (681 μm). The swelling is calculated as follows. Swelling = WS-Wd/Wd
   Where, Ws is the weight of hydrogels in swollen state and Wd is the weight of hydrogel in dry state
   Method B - In a volumetric vial the dry hydrogel (0.05-0.1g) was dispersed into sufficiently high quantity of water (25-30 ml) for 48 hrs at room temperature. The mixture is then centrifuged to obtain the layers of water bound material and free unabsorbed water. The free water is removed and the swelling can be measured according to Method A above.
   Method C - In method C the dry gel is immersed in deionized water for 16 h at room temperature. After swelling, the hydrogel was filtered using a stainless-steel net of 100- mesh (149 μm). Swelling is calculated as follows:-
   Swelling= C×100/B
   Where C is the weight of hydrogel obtained after drying and B is the weight of the insoluble portion after extraction with water.

5. **X-ray diffraction-** Diffraction analysis is the estimation of crystalline or amorphous characteristics. It is used to understand whether the polymers retain their crystalline structure or they get deformed during the processing pressurization process. The diffraction analysis is quite a popular study for the morphological characterization of hydrogels.

6. **In -Vitro drug release study-** Since hydrogels are the swollen polymeric networks, interior of which is occupied by drug molecules, therefore, release studies are carried out to understand the mechanism of release over a period of application. The parameters are matched with the standard plot so that the equivalence between the drug solutions is carried out.

7. **Rheology-** Viscosity of hydrogels is evaluated by using Cone plate type viscometer under constant temperature at 4ºC. This viscometer is highly specific for the evaluation of viscosity. The viscosity is determined by the simple equation of the angle of repose through that height and length is determined.

8. **Spreadibility study**- The apparatus was made of wooden block with scale and two glass slides having a pan mounted on a pulley. Excess formulation was placed between two glass slides and 100 gm weight was placed on upper glass slide for 5 minutes to compare the formulation to achieve uniform thickness. Weight can be added and the time to separate the two slides was taken as spreadibilty time.
   $S= (m \times l) / t$
   Where S is spreadibilty, m is weight tied on upper slide, l is length of glass slide and t is time taken in seconds

9. **Skin irritancy test studies -** Skin irritancy tests are conducted on rabbits. The preparation was applied on two rabbits and the area was protected with gauze or bandage. After 24 hours the formulation was removed and the area was checked for any signs of edema and erythema. Average irritation scores= (erythema reaction scores + edema reaction scores) / time interval.

10. **X-ray diffraction**- X-ray diffraction is used to understand whether polymers retain their crystalline nature or they get deform during pressurization process.

11. **Network pore size -** Pore size is measured by a number of technologies like electron microscopy, mercury porosimetry and others.

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