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HYDROGELS, THEIR APPLICATIONS AND POLYMERS USED FOR HYDROGELS: A REVIEW

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ABSTRACT

Skin is the largest organ of human body and drug delivery through this route is called transdermal drug delivery system. This route of drug administration is used for local as well as systemic delivery of drugs. Transdermal method of drug delivery is an alternate way of providing medications for controlled or sustained release as well as when orally or other methods of drug delivery are unavailable. With passage of time and interventions in the field of science and polymers a new class of drug delivery named hydrogels was formulated. Objective of writing this review is to provide the information and knowledge about hydrogels, polymers which are being used in formulation of hydrogels and their applications.Original research articles and review articles published in different peer review journal and various open access journals were reviewed for collecting the data and information about hydrogels, polymers and their applications to provide the readers comprehensive information about this impressive drug delivery system. Hydrogels are three dimensional cross linked structures. They can be prepared by using different natural and synthetic polymers. Hydrogels have the ability to retain a lot of water due to which they resemble natural tissues. From literature survey it is concluded that hydrogels are very impressive and effective formulation for delivering the drug with sustained effect without first pass effect providing maximum bioavailability to the patient with the ease of self-administration.

Keywords: Hydrogel, Semi IPN, IPN, Polymers,

INTRODUCTION

The trend of using skin as drug delivery system started a long time ago. But since early 1980s trasndermal drug delivery system is available in pharmaceutical market. Transdermal drug delivery system has many advantages over other routes of drug administration like a) by pass liver in terms of first pass metabolism b) convenient way of dosing c) therapy can be started and stop by the patient itself. Many transdermal dosage forms are available like gels, ointments, creams and etc[1]. Gels, gels are solid, jelly like material having a character of ranging from solid, hard to tough. Gels are defined as dilute cross linked system having no flow in steady state condition. Gels are further classified as hydrogels, xerogels and organogels[2A]. Hydrogels can be defined as polymeric networks capable of absorbing large quantities of water, but remains insoluble due to chemical or physical cross linking [2]. Hydrogels are 3 dimensional network systems. Formation of system occurs due to cross linking of polymeric chains. Cross linking may occur via physical interactions, covalent bonding, and hydrogen bonding or by van der wall interactions[3]. Hydrogels are smart enough that they can respond to envoirmental fluctuations like (Ph, temperature, ionic strength, electrostatic field and presence of enzyme) [4]. First hydrogel was prepared by professor Lim and Wichterle[5] of Czech Republic in 1955[6]. The hydrogel was prepared from a synthetic poly -2- hydroxyethyl methacrylate and used as contact lens. Hydrogels are used in biomedical disciplines, contact lenses, surgery, orally, transdermally and many other purposes [7-11]. Hydrogels can be prepared from either natural or synthetic polymers. Natural polymers include[2] dextran, alginate, and pectin and chondroitin sulphate[12]. While synthetic polymers include, poly(vinyl alcohol), poly(hydroxyethyl methacrylate) , poly(ethylene oxide) and poly (N-isopropylacrylamide)[12]. Either natural or synthetic polymers indivually have some advantages and disadvantages, but by combining natural and synthetic polymers the physical and biocompatibility properties like in IPN and semi IPN increase [13]. The ability of hydrogels to absorb water arises from hydrophilic functional groups attached to them[14]. They absorb 90 % of water due to which they resemble normal tissues [4]. Network structure of hydrogels can be macroporous, microporous and nanoporous. Macroporous size ranges from 0.1 to 1 micronmeter and drug release through diffusion method. Microporous having small pore size of 100- 1000 angstrom and drug release by molecular diffusion and convection. While nanoporous having a mesh size of 10-100 angstrom and release of drug is only by diffusion mechanism.[15]

Advantages of hydrogels

1. Posse's high degree of flexibility similar to natural tissues.
2. Bio compatible, bio degradable and that is why they can be injected.
3. They may be PH or temperature sensitive and release drug upon such changes.
4. Applied locally so by passing first pass metabolism [16]

Disadvantages of hydrogels

1. PNIPAAm based hydrogels are temperature sensitive hydrogels. They can cause excess or less amount of drug release in accordance with temperature stimuli [17]
2. They cause a sensation due to the movement of maggots
3. In case of contact lenses cause lens deposition, hypoxia, dehydration, and eye reactions [18]

Methods of preparation of hydrogels

1. Homopolymer hydrogel

A polymer network derived from single species of monomer. These hydrogels are cross linked structure depending upon monomer and polymerization technique. These types of hydrogels can be used for transdermal drug delivery system and for ophthalmic purposes [19]. Homopolymers may be cross linked or uncross linked. It depends upon the nature of monomer and polymerization technique used. Homopolymers which are cross linked are used as slow drug deleivery and in contact lenses. They include poly 3-hydroxypropyl methacrylate (PHPMA) and poly glycerol methacrylate (PGMA). Homopolymers which are uncrossed linked are poly N-vinyl

2 pyrrolidone (PNVP) and polyvinyl alcohol (PVA). PNVP is very helpful in medicine because it is highly water soluble. PVA is also very helpful in biomedical and agricultural applications [20-24]. Poly (2-hydroxyethyl methacrylate) is used as monomer, polyethylene glycol dimethacrylate as cross linking agent and benzoin isobutyl ether as initiator. These types of hydrogels are used in contact lenses [16]. Polyvinyl pyrollidone , polyacrylic acid , polyvinyl alcohol and polyethylene glycol are also used for homopolymer based hydrogel preparations [16].

2. Co polymeric hydrogel

In these hydrogels two types of monomers are used, from which at least one is hydrophilic in nature [25]. There is a wide range of important copolymeric hydrogels with combination of compatible monomers they include poly(NVP-co-HEMA), poly(HEMA-co-MMA) and others [26-28]. Preparation of a tri block of polyethylene glycol, poly Є caprolactone, polyethylene glycol. Involving the mechanism of copolymerization of Є caprolactone[25].

3. Semi inter penetrating networks (semi IPN)

In this type of hydrogels one polymer is linear and penetrates without any bond inside the crosslinked network without any chemical bond. They are beneficial due to modification in pore size and slow drug release [16, 29]. Semi IPN of alginate and amine terminated poly (N-isopropyl acrylamide) PNIPAAm were synthesized by using calcium chloride as cross linking agent. These hydrogels are sensitive against temperature and pH [30]. N, N, methylenebisacrylamide is used as a cross linking agent, ammonium persulfate as initiator, trisodium citrate as reducing agent, cross linked polymer is PHEMA. Semi IPN of gum Arabic prepared by loading silver nitrate which Shows excellent anti bacterial activity [31]. One of the semi IPN is the incorporation of linear cationic polyallyl ammonium chloride in acrylic or acrylamide co-polymer hydrogel [16].

4. Inter penetrating networks (IPN)

They are the combination of two polymers. From which at least one is synthesized or cross linked in the presence of other. In this type of reaction method a polymerization initiator and suitable monomers are placed in a solution and then immersing a pre polymerized hydrogel completes the reaction method. This method produced hydrogels which are stiffer, tougher mechanical properties and more efficient drug loading than conventional methods of hydrogel preparation [16]. Poly (ethylene glycol) diacrylate hydrogels are modified by adding β-chitosan. The hydrogel is formulated by adding10% aqueous solution of Polyethylene Glycol diacrylate into 2% solution of chitosan in acetic acid. Then cross linked by UV radiation to form hydrogel. This type of hydrogel contains 77-83% of water [32]. IPN hydrogels have much more faster shrinking and gaining swelling characters then the other two network components. These fast responsive hydrogels made them suitable for applications in biomedical fields [32].

Hydrogels in drug delivery

Hydrogels now a day are more attracted because of their controlled as well as sustained release of drugs. They are able to release the drugs at suitable and targeted sites. Hydrogels are utilized in a number of ways as described below [15].

1. **Wound healing**

Hydrogels are cross linked materials they have the ability to hold water and drug in them. Due to their water holding ability they can hold and retain wound exudates. Gelatin and sodium alginate based hydrogels when applied have the ability to cover and protect the wound from bacterial infection [33].

2. **Hydrogels for eye**

Hui and robinson were the first to make bioadhesive based ocular drug delivery system [34]. According to estimation 75 % of ophthalmic solution is lost due to the nasolacrimal drainage and the desired bioavailability of the drug decreases[35]. Some other factors like the blinking tear drainage also effects drug bioavailability. Mishra and co-workers worked on P (NIPAAM-co-dex-lactate HEMA) for the release of insulin in rat eye. These hydrogels are 100 % safe and are implanted under conjunctiva [36]. Xyloglucan based gel is used for sustained deleivery of pilocarpine and timolol in eye[15].

3. **Hydrogels for transdermal drug delivery**

Hydrogels when utilized by topical / transderm have many advantages like they bypass the hepatic metabolism, thus increases drug efficacy and bioavailability [37]. For achieving a constant drug release transdermal drug delivery system is used. Hydrogels as they are swollen and resemble living tissues can be easily removed rather than the other dosage forms like patches, ointments. Transdermal drug delivery is used to administer drugs systemically as well as for topical disorders like for delivery of gluocorticoid budesonide transdermal hydrogels are prepared[38]. Poloxamer 407 based novel hydrogels containing gentamycin are more effective in treating skin infections, rather than the gentamycin parentral administration causing serious disorders[39].

4. **Vaginal route**

Drugs to be administered through vagina must be in the form of like creams, suppositories, gels, foams or tablet formulations [40]. Vaginal route of drug administration have many advantages of by passing the hepatic metabolism. Due to the large surface area of vagina there is an increase in the systemic drug absorption. Drugs with high molecular weights are permeable due to vaginal epithelium. Natural progesterone's bioavailability decreases due to the hepatic metabolism so vaginal route is the preferable one [37]. Flat faced disk containing bleomycin anticancer drug crosslinked with carbopol 934 and hydroxypropyl cellulose releases the drug for over 23 hours [40].

5. **Oral route**

Oral route have many advantages like it is easily accessible. Oral route is used for local viral and fungal infections. This route also reduces the first pass metabolism[40]. A mucosal adhesive tablet of lidocaine was formulated by combining carbopol 934, hydroxypropyl cellulose, and magnesium sterate. Tablet having a diameter of 1 cm and thickness of 2 mm [40, 41].

6. **Gastro intestinal tract**

G.I tract is most common and popular route of drug administration. G.I tract is also used to deliver drugs locally.Famotidine anti-ulcer drug used for local effects. Sustained release gastro retentive hydrogels are made to increase the effects and bioavailability of poorly absorbed oral drugs[42].

7. **Hydrogels for brain**

Like other barriers in human body, blood brain barrier is also a challenge for drug delivery. About 98 % of the newly synthesized drugs fail to cross this barrier. Due to that reason a low number of drugs are present for drug delivery for CNS.Long term sustained effect of camptothecin loaded with PLGA microspheres was observed in rats. These microspheres increase the survival period in rats against malignant gliomas[35].

Evaluation parameters for gel

1. pH

P.H of hydrogels is measured by using digital P.H meter. P.H meter must be calibrated before its use [43].

2. Viscosity

Viscosities of hydrogel are measured by using Brookfield viscometer [44].

3. Spreadibility study

Mutimer et al suggested a apparatus to measure the spreadibility of hydrogel in laboratory. 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 spreadibility time.

S= (m × l) / t

Where S is spreadibility, m is weight tied on upper slide, l is length of glass slide and t is time taken in seconds[45].

4. Skin irritancy test studies

Hydrogels are used for dermal application that is why skin irritancy test is important. 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

Based on scoring graded as

Non irritant

Irritant

Highly irritant

Irritation scores based on extent of edema and erythema as

0 = for no visible reaction

1 = for just present reaction

2 = for slight reaction

3 = for moderate reaction

4 = for severe reaction[46, 47]

5. Atomic force microscopy

The surface morphology of the hydrogels is studied by multimode atomic force microscope[48].

6. X-ray diffraction

X-ray diffraction is used to understand whether polymers retain their crystalline nature or they get deform during pressurization process [48].

7. Network pore size

Pore size is measured by a number of technologies like electron microscopy, mercury porosimetry and others[48].

8. Solubility

Hydrogel solubility content can be measured by immersing product in deionized water for 16 hours (Katayama , Nakauma et al 2006) or 48 hours at room temperature (Nagasawa et al 2004). Sample should be prepared in dilute concentration approximately 1% to ensure hydrogel fully disperse in water. Gel fraction can be measured as follows[49, 50];

Gel fraction (hydrogel %) = $(W_d / W_i) \times 100$

Where W_i is initial weight of dried sample and $W_d$is weight of dried insoluble part after extraction with water

9. Swelling measurement

Japanese industrial standard k 8150method has been used to measure the swelling of hydrogels. In this method hydrogel is immersed in deionized water for 48 hours at room temperature on a roller mixer. After swelling gel is filtered by using stainless steel net of 30 meshes (681 µm), swelling is calculated by (Nagasawa et al 2004)[50]

Swelling = $(w_s - w_d) / w_d$

Where $W_s$is weight of hydrogel in swollen state and W_d is weight of hydrogel in dry state.

10. F.T.I.R

Fourier transform infrared spectroscopy is a technique used to identify the chemical structure of a substance. Based on principle that the basic components like chemical bonds may be excited and can absorb infrared light at frequencies that are typical of the types of the chemical bond .FTIR is usually widely used to investigate structural arrangements before starting experiments.(Mansur et al 2004 , Torres et al 2003)[51, 52].

Hydrogels as smart polymers

Now a day a more attention is given to smart polymers as drug carriers because they suit fit for drug delivery system.For this purpose hydrogels are best option because they are biocompatible, resemble natural tissue and release drug in a controlled manner[53]. Smart polymers are polymers that change accordingly by a number of factors like P.H, temperature, humidity, intensity of light, electric field and magnetic field. Smart polymers are currently used in drug delivery system due to their nature.

Hydrogels composed by cross linking of poly (N-isopropylacrylamide-co-acrylamide) or poly (N-isopropylacrylamide)their pore size changes with the change in temperature[54]. A table given below clarifies the smart polymers which are used in hydrogels[53].

Polymers in hydrogels

Polymers are present everywhere naturally or synthetically. Human body is also made up of polymers like protein, enzymes and others."Poly" means "many" and the" mer" is originated from Greek language means "meros". So as a whole it means "consisting of many parts".

The first ever made semi-synthetic polymer was cellular nitrate and made by Christian F. Schunbein in 1845. Now a day's polymers are used for controlled drug delivery, replacing natural organs, by passing the harsh stomach envoirment and other applications [20A].

Function of polymers

The main function of polymers is to prevent the drug from interaction between the proteins and other macromolecules and release the therapeutic agent at required or targeted site [53].

Classification of polymers

1. **Water soluble synthetic polymers**

Water soluble synthetic polymers contain hydrophilic functional groups in them like an ester, amide or pyrollidone. These polymers are often bio compatible and nontoxic. These polymers include. Polyethylene glycol, polyvinyl pyrollidone , poly acrylic acid and polyacrylamide [55].

Poly acrylic acid

Poly acrylic acid or carbomer, these are synthetic and high molecular weight polymers of acrylic acid. carbomer are coded as 934, 934 P , 940 , 910.[21A] When these polymers are used for making hydrogels they have the ability to absorb a lot of water many times greater than their weights. On the basis of retaining high water quantities they are called super absorbants[56]. The reason behind the absorption of large quantities of water is that these polymers lose their protons and acquire a negative charge. And absorb water[21A]. Hydrogels of grisofluvin for topical application were prepared by using carbopol 940. These hydrogels provide better drug availability because oral bioavailability of grisofluvin is poor[57]. Carbopol 974P were used to formulate vaginal based liposome's containing acyclovir. These liposomes were used for local therapy of gynecological disorders[58].

Polyethylene glycol (PEG)

PEG is a water soluble polymer[55]. PEG used in hydrogels due to its biocompatible, nontoxic and water soluble properties. PEG based hydrogels are called "smart polymers" or "intelligent gels" because they are stimuli based hydrogels. The stimuli may be physical (temperature, solvent, light, radiation, pressure) or chemical (PH, specific ions). These hydrogels are also used for controlled release of drugs[6].

Polyvinyl alcohol (PVA)

PVA is also a water soluble polymer. Due to its water retainability and biocompatibility it is used as scaffold for tissue cultures, contact lenses[6, 55], cartilage reconstitution[55] and wound dressing [6].

PVA based hydrogels are obtained by freezing and thawing process. In 1962 winter mentioned the use of moist dressing for wound care which was then later confirmed. Due to high water retention PVA hydrogels are used in wound dressing.Silver is used to prevent and treat a lot of infections and disease. So KIM et al prepared PVA based hydrogels having silver incorporated nanoparticles having anti-bacterial activity. PVA are also used as scaffolds due to good hydrophilicity and chemical stability [55].

Polyvinyl pyrollidone (PVP)

PVP is soluble in water as well as in polar solvents[55]. PVP is used in wound dressing because of storing large quantities of water, low production cost and good elasticity properties. PVP in combination with other polymers like CMC are also used to enhance mechanical properties and biocompatibility. Retaining high quantity of water PVP are also used in making contact lenses. NOH et al investigated soft contact lenses of PVP-g-HEMA[6].

Polyacrylamide

It is also a water soluble polymer. ZHAN et al develop poly acrylamide beads for biotechnology uses[55].

2. **Cellulose derivatives**

Cellulose is present in higher plants as their main constituent. Cellulose is insoluble in water and other solvents. The insolubility is due to hydrogen bonding present between them. But its water soluble derivatives are used extensively in pharmaceutical applications [20A]. Commercial cellulose ethers include Carboxymethyl cellulose (CMC), Hydroxypropyl methyl cellulose(HPMC) , hydroxyethyl cellulose(HEC) [59]. HPMC and MC have thermo gelling property in water [20A]. HPMC K15M based hydrogels containing silver in them are used as antimicrobial activity[60]. Hydrogels like CMC and PVP with and without boric acid are investigated for antimicrobial properties[61].

3. **Hydrocolloids**

Most of the gums are hydrophilic due to which they are extensively used in pharmaceutical processes. Gums have thickening and gelling properties, thickening property is suitable for emulsions and suspensions while gelling property is beneficial for controlled drug delivery. Guar gum shows thickening while chitosan shows gelling property. One of the negative aspects of gums is that they provide a good platform for microbial growth [20A].

Alginate

Alginate is a linear polysaccharide extracted from brown[59] sea weed and algae[42]. Alginate is made up of (1-4)-b-D-mannauronic acid and (1-4) –a-L-gluronic acid[42]. In presence of ions they undergo complexation reaction due to presence of carboxylic group [20A]. Gelling property of alginate is due to the presence of G block [20A]. Biodegradability, low toxicity and non-immunogenicity[42] made alginate a suitable candidate for used as a binding agent[20A], drug carrier[20A], controlled release of drugs and proteins[42]. Hydrogels containing famotidine for stomach targeting are formed by incorporating sodium alginate and polyacrylamide by grafting technique[42].

Carrageenan

Hydrocolloid obtained from red sea weed[62]. Carragennan consists of galactose as well as anhydrogalactose [20A] and used in sustained release dosage forms. Carrageenans present in three different grades Kappa, Iota and Lambda[62].

Kappa forms strong gel, Iota forms soft gels while both kappa and iota are used for controlled release drug delivery. For thickening of a drug formulation Lambda carrageenan is used.[20A]

0.5-1 % concentration of carrageenan is used for making gels. Other preparations include tooth pastes, creams and cosmetic products.[62]

Chitosan

Chitosan is a natural polymer can be obtained from shrimp, crab and lobster shell [20A]. It is a cationic polysaccharide[62][20A]. Mostly chitosan is obtained by deacetylation of chitin[59]. Chitosan is made up of glucosamine and N-acetyl glucosamine units.[59]

Chitosan is biodegradable , biocompatible , and non toxic due to which it is used in pharmaceutical applications like[59] drug carrier[20A] , tablet excipient[20A] , gel former [62], powder , and in emulsion.[59]

Chitosan is also used for veterinary purposes like for delivery of chemotherapeutics, pain killers, and antibiotics.[20A]

A thermo and PH sensitive based hydrogel of chitosan were prepared containing doxorubicin hydrochloride as a model drug. These hydrogels were formulated to study the release of drug at different ph.[63]

Hyaluronic acid

Hyaluronic acid is also called hyaluronan and hyaluronate (HA) or sodium hyaluronate[59]. It is a N-acetyl-D- glucosamine and beta gluronic acid [20A]. HA is a naturally occurring polymer and found in tissues of higher animals [59], as well as in vitreous of eye, and in synovial fluid.[59]

It is used in nasal, pulmonary parenteral and ophthalmic preparations due to its biocompatibility and non immunogenicity properties.[20A]

HA based hydrogels are used for delivery of therapeutic agents for tissue repair. Due to its visoelastic property [59, 64]it can be utilized for stiff or soft hydrogels , non woven meshes , flexible sheets and for drug targeting.[59, 64]

4. Natural polymers

Natural polymers include the following

Gelatin

Gelatin is a water soluble natural polymer[59]. Gelatin is produce by the hydrolysis of collagen obtained from connective tissues and bones of animals [20A]. Gelatin is soluble in a hot mixture of glycerol and water and insoluble in alcohol, chloroform and oils.[20A]

Gelatin is used for gene delivery, cell culture and protein delivery. [59]

Hydrogels based wound dressings consist of sodium alginate and gelatin were prepared by crosslinking of sodium chloride / glutaraldehyde. These hydrogels are nontoxic and shows better results when gelatin and sodium alginate are in equal proportions.[33]

Dextran

Dextran is a natural polymer synthesized from sucrose. Due to its water solubility, biocompatibility and unique properties it is used for sustaining the effects of proteins, interleukin-2 and other drugs.

Stenekes and coworkers encapsulated a drug loaded liposomes with dextran having a capability of sustaining the effects for 100 days.[59]

A lot of methods are developed to ensure wound healing to become rapid and less painful. Dextran based hydrogels having chitosan microparticles are loaded with growth factors to ensure rapid wound healing.[65]

Paclitaxel an anti-cancer drug is used to make dextran based hydrogels. These hydrogels are PH sensitive and are utilized for colon targeting.[66]

Xanthan gum

Xanthan gum is produced by fermentation of carbohydrate with xanthomonascampestris. It is a cream colored powder soluble in hot as well as cold water. Xanthan gum is stable over a range of PH 4-10.[62]

Having both thickening and swelling property so it is used in suspensions due to thickening and in morphine based rectal hydrogels due to swelling property.[20A]

Superporous hydrogels were prepared by using xanthan gum, acrylic acid and 2-hydroxyethyl methacrylate (HEMA) by graft copolymerization technique.[67]

5. **Starch based polymers**

Starch

Starch is synthesize and stored by all plants for energy purposes. Available in the form of small granules ranging in size from 1-100 micro meters. Starch is a biodegradable polymer due to which it has pharmaceutical applications [59]. PH sensitive based hydrogels were prepared by using starch and methacrylic acid by copolymer method loaded with ketoprofen as a model drug [68].

Hydrogels in pharmaceutical market

With the passage of time new interventions are made in field of pharmaceuticals. Researchers are keen to provide patient compliance regarding the use of medicines. So a lot of research has been conducted on hydrogels and some of the items are available in market while some others are in the way for approval. Lists a number of available hydrogels.[35]

Table 1: Examples of different routes of administration of gels, polymers and drugs used

Sr.No	Therapeutic system	Polymer	Drug	Reference
1	Oral cavity	Carboxy vinyl	17-b-estradiol	[69]
2	Gastro intestinal tract	Freeze dried chitosan -poly ethylene oxide	Amoxicillin and metronidazole	[70]
3	Rectal delivery	Polycarbophil and sodium alginate	Propanolol	[71]
4	Ocular delivery	Hyaluronic acid	Latanoprost	[72]
5	Transdermal	Hydroxylpropyl methylcellulose	Ketoconazole	[73]
6		HPMC k 15 M, carbopol 934 P , xanthan gum	Lornoxicam	[74]
7	Subcutaneous	Poly(hydroxyethyl methacrylate bis glycol acrylate)	5-flurouracil	[75]
8	Vaginal	Carboxymethyl cellulose-sodium , carbopol 940 , poloxamer	Clotrimazole	[76]
9	Dental care	Carbopol	Diclofenac and metronidazole	[77]

Table 2: Examples of smart polymers being used as gelling agent

Stimulus	Polymer	Drug released
pH	Poly(methacrylic-g-ethylene glycol) (p(MMA-g-EG)	Insulin
Electric field	Poly(methacrylic acid) (PMA)	Pilocarpine and raffinose
Glucose concentration	Poly(methacrylic acid-co-butyl methacrylate)	Insulin
Temperature	Layer of Chitosan Pluronic on PLGA microparticles	Indomethacin
Morphine concentration	Methyl vinyl ether-Co-anhydride maleic copolymer	Naltrexone
Urea concentration	Methyl vinyl ether-Co-anhydride maleic copolymer	Hydrocortisone

Table 3: Examples of polymers used in gel formulation and their application

Polymer	Characteristics	Applications
Cellulose derivates		
Methyl cellulose	Soluble in cold water only[20A]	Polymer based hydrogels are used in tissue engineering applications[78]
Ethyl cellulose	Insoluble in water[20A]	Used as coating for sustained release[20A]
Carboxymethyl cellulose	Soluble in water[20A]	Due to biocompatibility used in bioengineering field. CMC based hydrogels are use as scaffolds for controlled release devices[79]
Hydroxyethyl cellulose	Soluble in water and alcohol[20A]	Hydrogels are used as scaffolds for regenerative medicine. Also used as thickener and emulsifying agent[80]
Hydroxypropyl methyl cellulose	Water soluble[20A]	Used as gelling agent[20A]. HPMC has low toxicity and broad compatibility profile so it is used in ophthalmic and transdermal hydrogels other applications include thickening agent , binder and disintegrant[81]
Water soluble synthetic polymer		
Polyacrylic acid	Water soluble[21A]	Used as a thickening , suspending and emulsifying agent in pharmaceuticals [21A]
Polyethylene oxide	A hydrophilic and water soluble polymer[82]	PEO based hydrogels synthesize in water so they are examined artificial pancreas because of their semi-

		permeable and biocompatible nature[83]
Polyethylene glycol	Soluble in water[84]	Polymer based hydrogels are used for enzyme immobilization[85]
Polyvinyl pyrollidone	Water soluble polymer[86]	Used for biomedical applications[87]
Polyvinyl alcohol	Soluble in water[88]	PVA based hydrogels are utilized in damaged cartilage replacement and also in orthopedic applications[88]
Polyacrylamide	Due to monopolar surface nature soluble in water[89]	Gels are used biomaterial[90]
Hydrocolloids		
Alginic acid	Soluble in water[91]	Hydrogels are used as co-transplantation on rat spinal cord injury[86]
Carragenaan	Water soluble[92]	Used as thickening , stabilizing and gelling agent[92]
Chitosan	Sparingly soluble in water [93]	Chitosan used in biomedical applications in drug delivery system and wound healing. Chitosan scaffolds are also prepared[87]
Hyaluronic acid	Most hydrophilic polymer in nature[94]	Its injectible hydrogels are prepared in combination with alginic acid for delivery of cell vehicle[95]
Starch based polymers		
Starch	Starch is insoluble in cold water[22A]	Used as a pharmaceutical excipient as a tablet superdisintegrant and also used as a sustained release polymer[96]
Natural polymer		
Xanthan gum	Soluble in hot as well as cold water[62]	Used as an emulsifier, thickener and stabilizing agent. Xanthan based gels are better than CMC.[62]
Dextran	Highly water soluble[97]	Dextran hydrogels are use in a number of applications like implants , scaffolds , PH and stimuli responsive hydrogels[97]
Gelatin	Soluble in water[59]	Gelatin is also used as gelling agent , in biomedical field , wound dressing and drug delivery system [98]

Table 4: Hydrogel available in the market

Hydrogel	Component	Purpose	Availability
Acuvue 2	Silicone hydrogels	Contact lens	In market
Tretin x gel	HPC , butylated hydroxyl toluene and alcohol	Acne vulgaris	In market
PEG hydrogel	PEG loaded with insulin	Improved cell viability	Preclinical trials
PVA hydrogels	PVA having properties of articular cartilage	Replaces articular cartilage	Pre-clinical trials
PVA hydrogel	PVA , nacl and DMSO/ water	For minimally invasive surgery (MIS)	Clinical stage

CONCLUSION

Finally it was concluded that gel/hydrogel is a suitable drug delivery system for the delivery of various drugs that cannot be delivered through other dosage form. It is a safe, effective and self-administrable drug delivery system that is appealing for the patient. It has enhanced the patient compliance by various means and aspects.

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