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Hydrogel: As Advance Drug Delivery System

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Review Article

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Abstract: Hydrogels have high affinity to absorb water due to the presence of hydrophilic group; Hydrogels can be prepared from both natural and synthetic polymer. Though the synthetic polymers are preferred more due to their less risk of immune response and less chances of viral and bacterial attack With increasing efforts devoted to controlled release of drug molecules, the application of hydrogels will continue to grow in future with its more relevantly and more efficiently applications, The success of hydrogels as delivery systems can be judged by several marketed preparations.

Keywords: Gel**;** Hydrogel; Polymer; Drug; Delivery; Control Release.

INTRODUCTION

The term hydrogel was coined to describe a gel which gets swollen by water or by aqueous solution (e.g., body fluids) [1-3]. Hydrogels are 3-dimensional cross-linked, hydrophilic polymeric structures that can be imbibing large amount of water or biological fluids [4]. They are soft and rubbery in the swollen state and are excellently biocompatible [5]. In the search of drug delivery, hydrogels are of immense importance [6-9]. Hydrogels have the minimum tendency to absorb portion from body fluids because of their low interfacial tension. Different terms have been coined for hydrogels such as 'intelligent hydrogels' & 'smart hydrogels' [10] in the surse that they can prescience the prevailing stimuli and respond by exhibiting changes in their physical & chemical behaviour which ultimate results in the release of entrapped drug in a controlled way. Hydrogels deriving from biocompatible polymers find wide application in the biochemical field [5, 11, 12].

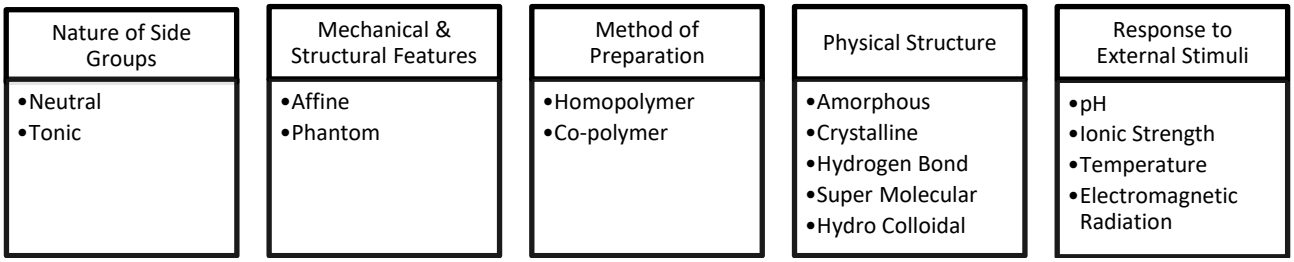
The polymeric networks are composed of homopolymers or co-polymers which are insoluble due to presence of chemical cross linked (tie prints, function); or physical crosslink's (entanglements, crystallites) [13, 14]. Due to thermodynamic compatibility with water, they can swell in aqueous media [15]. In particular, hydrogel pH-sensitive are widely used because of variations in pH that are known to occur at several body sites. Hydrogels bearing acid groups were used to develop formulations that release drugs in neutral pH environment. Hydrogels in the nano size range are referred as Nano gels and in the micro size range are referred as microgels [2].

Overview

Hydrogels have high affinity to absorb water due to the presence of hydrophilic group such as –OH, -$CONH_2$, -CONH, -SO_3H etc. [11, 12]. The presence of such groups hydrates the polymer to different degree depending upon the nature of aqueous environment and polymer composition [17]. These hydrogel exhibit a thermodynamic compatibility with water which allows then swell in different aqueous media [16, 18].

Classification

Generally hydrogels can be classified based on different characteristics such as-



The Polymer which are commonly used in preparation of hydrogel with pharmaceutical & biological application are from natural or synthetic origins [19-22]. As mentioned formerly, the water contents plays a main role in determining the overall characteristics of a polymeric network. The swelling property of hydrogel may also be induced due to the change in external physiological condition, where the polymer complexes are broken. Some factors affecting the swelling of physiological responsive hydrogel are- pH, ionic strength, temperature & electromagnetic radiation.

Gel vs. Hydrogel

A common confusion may occur in polymer science between the 'gel' and 'hydro gel'. Sometimes there is a misinterpretion in the use of the term 'aqueous gel' and 'hydro gel' because of the term 'hydro'. But, as polymeric network both gels & hydro gels might be similar but they are physically distinct. Dorothy Jordon Lloyd described gels as, "The colloidal condition, the gel, is one which is easier to recognise than to define" [22]. Technically, gels are semisolid systems comprising small amount of solid dispersed in large amount of liquids; yet possessing more solid like character than liquid like [23]. In true sense, hydro gels are a cross linked network of hydrophilic polymers which possesses the ability to absorb large amount of water and swell, maintaining their 3-dimensional (3D) structure.

DEFINATION OF HYDROGELS

Inorganic	It constitutes of two phase system
Organic	It usually constitutes of a single phase system.
Organ gels	It is of hydrocarbon type, constitute of animal fats, vegetable fats, Soap base grease.
Hydro gels	They are of organic either natural or synthetic gums and also inorganic hydro gels and it shows most biocompatibility and resembles the biomembrane.

The above definition differentiates gels from hydrogels when the former are polymeric network already swollen to equilibrium, and the further addition of fluids results only in dilution of the polymeric network.

Natural polymers and their derivative

Anionic polymers	HA, Alginic acid, Pectin, Carrageenan, Chondroitin sulfate, Dextran sulfate
Cationic polymers	Chitosan, Polylysine
Amphipathic polymers	Collagen (and gelatin), Carboxymethyl chitin, Fibrin
Neutral polymers	Dextran, Agarose, Pullulan

SYNTHETIC POLYMERS

Polyesters	PEG–PLA–PEG, PEG–PLGA–PEG, PEG–PCL–PEG, PLA–PEG–PLA, PHB, P (PF-co-EG) 6 acrylate end groups, P(PEG/PBO terephthalate)
Other polymers	PEG-bis-(PLA-acrylate), PEG6CDs, PEG-g-P (AAm-co-Vamine), PAAm, P(NIPAAm-co-AAc),P(NIPAAm-co-EMA),PVAc/PVA,PNVP,P(MMA-co-HEMA),P(AN-coallylsulfonate),P(biscarboxy-phenoxy-phosphazene), P(GEMA-sulfate)

Combinations of natural and synthetic polymers

Hydrogels can be prepared from both natural & synthetic polymer. Though the synthetic polymers are preferred more due to their less risk of immune response & less chances of viral and bacterial attack. P (PEG-co-peptides), alginate-g-(PEO–PPO–PEO), P (PLGA-co-serine), collagen-acrylate, alginate-acrylate, P (HPMA-g-peptide), P (HEMA/Matrigel®), HA-g-NIPAAm [2, 24].

MONOMERS COMMONLY USED IN SYNTHESIS OF SYNTHETIC HYDROGELS FOR PHARMACEUTICAL APPLICATION

Sl. No.	Monomer chemical name	Monomer abbreviation
1	Hydroxyethyl methacrylate	HEMA
2	Hydroxyethoxyethyl methacrylate	HEEMA
3	Hydroxydiethoxyethyl methacrylate	HDEEMA
4	Methoxyethyl methacrylate	MEMA
5	Methoxyethoxyethyl methacrylate	MEEMA
6	Methoxydiethoxyethyl methacrylate	MDEEMA
7	Ethylene glycol dimethacrylate	EGDMA
8	N-vinyl-2-pyrrolidone	NVP
9	N-isopropyl Aam	NIPAAm
10	Vinyl acetate	VAc
11	Aacrylic acid	AA
12	Methacrylic acid	MAA
13	N-(2-hydroxypropyl) methacrylamide	HPMA
14	Ethylene glycol	EG
15	PEG acrylate	PEGA
16	PEG methacrylate	PEGMA
17	PEG diacrylate	PEGDA
18	PEG dimethacrylate	PEGDMA

SYNTHESIS OF HYDROGEL

Generally, hydrogels are synthesized by crosslinking method in which crosslinking occurs between the monomers, cross linkers, and initiators. Khutoryanski et al., [27] reported a method to synthesise hydrogels from ready-made water soluble polymersin aqueous solution using thermal treatment or microwave radiation (ϒ Radiation, x-ray etc.). The major procedures for the manufacturing of hydrogels in semi-pilot and industrial scales can be represented by the block diagram of a generic solution polymerization process [26]. Radiation and thermal crosslinking methods are inexpensive and safe. Purification of hydrogels is not required if a suitable Combination of hydrophilic polymers used [27].

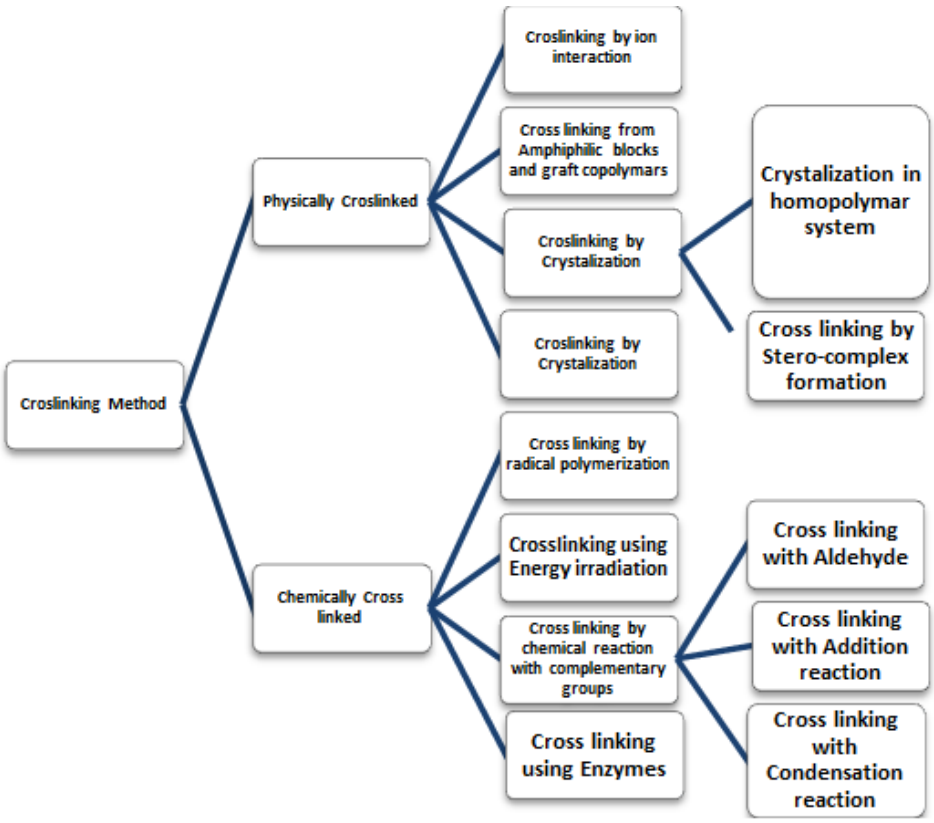


FIG-1: NOVEL CROSSLINKING METHODS USED IN HYDROGEL

CHEMICALLY CROSS-LINKED HYDROGELS

Radical polymerization technique which is based on addition and are commonly used for the preparation of polymers which is subsequently transformed into hydrogel by moderate crosslinking of the polymer chain in aqueous solution. In this way swollen gels are swelled up by the addition of water molecules to an equilibrium swelling and attached themselves to the hydration layer and loosely cross-linked polymeric chains is driver aside, the swelled gels are reached to an equilibrium state when the energy and entropy are losses due to stretching of polymerized chain. The preparation of chemically cross-linked hydrogel includes modulate aqueous solution of two or more than two polymers i.e. co-polymers in which the segments is embedded with hydrophilic groups. Crosslinked may also be due to the chemical interactions of the functional groups of the polymers [28]. The equilibrium of swelled gel is maximal in acidic (for bases) and basic (for acid) solution and subsequently decreases with the decreases in acidity & basicity acid co-polymers, on their mechanical & thermodynamic properties, was extensively investigated by Ketime et al. [29,30]. Valles et al. [31] also investigated the effect of these factors on polymers and co-polymers of it a conic acid and its derivatives. The preparation of hydrogels of polyvinyl alcohol (PrA), polyhydroxy methocrylate (PHEMA), polyacrilamides, chemically modified chitosans and methacrylic acid (MA) is described by the following examples

- Peppas NA *et al*., [32] prepared PVA hydrogel by electron beam radiation of the commercial PVA. Direct crosslinked was due to the formation of polymeric radicals the indirect effect was due to hydrogen and hydroxyl radical released by the irradiated water.
- Bader *et al*., [33] proposed another method using photopolymerization by crosslinked PVA modified by grafting 1, 2-epoxy-5-hexane onto it.
- Cretu *et al*., [32] prepared a biodegradable hydrogel by a macromer incorporating few HEMA groups into poly (L-lactide).
- Yang *et al*., [34] prepared PVA-chitoson hydrogel by ϒ-radiation combined with thawing a concentrated aqueous solution of a homogenous aqueous solution containing 7% of PVA and soluble chitosan hydrochloride obtained by protonating chitosan with HCL in ethanol.
- Lee *et al*., [35] dissolved chitosan in aqueous solution of acrylic acid to prepare chitosan/poly (acrylic acid) IPN hydrogel.
- Garcia *et al*., [36] synthesized poly-methacrylic acid hydrogels by using free radical polymerization of concentrated aqueous solution of methacrylic acid (MA) in the presence of crosslinker (N, N' metheylene bisacrylamide).

PHYSICALLY CROSSLINKED HYDROGELS

These hydrogels are formed spontaneously under appropriate conditions. They do not require introduction of external introduction of external crosslinked agent, which are usually non-degradable and may prevent the degrading ability of the entire hydrogel. Moreover, the crosslinked agents are often toxic, and required removal of traces amount of residues. Physical crosslinked hydrogels are also advantageous as they are usually biodegradable [28]. Wu *et al*., [37] prepared physically crosslinked hydrogels from PVA and amine terminated polyamidomine dendrimer described is based on freeze-thaw method proposed by Hyon *et al*., [38].

The following examples illustrate the method of preparation of hydrogels

- Wu *et al*., [37] prepared separately 10% aqueous solution of PVA and G6-NH_2, mixed them at 2:1 (v/v) ratio, and cooled the PVA/G6-NH_2 mixture at -20^0C. After 23 hrs the mixture warmed back to 25^0C. The swelling ratio of hydrogel prepared in this manner was 15:5:1 compared to 14:1 for PVA only using an indicated freezing thaw procedure.
- Hyon *et al*., [38] prepared transparent PVA hydrogel by keeping 15 %w/v solution of PVA in Duso/H_2O solvent mixture at 140^0C. The hydrogel prepared in this manner absorb 85 %w/v of water.
- An alternative freeze thaw procedure was proposed by Nugent *et al*., [39].
- Misumeta *et al*., [40] prepared physically crosslinked hydrogels of PVA combined with sodium silicate (SS) whereas Xiao & GAO [40] prepared with CMC.
- Hennick *et al.*, [42, 43] prepared hydrogels hydrogels through complexation of the enantiomers of opposite chirality of the oligomers of lactic acid coupled with dextran.
- Chung *et al*., [44] also prepared stereocomplexed, physically crosslinked hydrogels by linking multiblock pluronic copolymers with the (D)-lactate & (L)-lactate oligomers.
- Mequanint *et al*., [45] prepared physically crosslinked copolymers hydrogels from polyurethane macroiniferter through controlled radical polymerization by coupling with (2,2'-dimethyl-1,3-dioxolane) methyl methacrylate (DMDOMA).
- Patel & Mequanint [46] synthesized physically crosslinked hydrogels by coupling polyurethane co-polymers coupled with poly (vinyl chloride).
- Nam *et al*., [47] used two water soluble co-polymers containing water soluble phospholipid groups such as the 2-methacryloyl oxyethyl phosphoryl choline (MPC) and either methacrylic acid or butyl methacrylic acid or butyl methacrylic acid to prepare physically bounded hydrogels.

DEVELOPMENT OF HYDROGEL BASED DRUG DELIVERY SYSTEM

Preparation of hydrogel based drug products involves either crosslinked of linear polymers or simultaneous polymerization of monofunctional monomers and crosslinking with polyfunctional monomer [48, 49]. Again the mechanical strength of poorly crosslinked hydrogel can be adequately enhanced by various methods [50]. Usually polymers from natural source, synthetic polymers containing hydroxyl groups, amine, amide, ether and carboxylate as functional groups in their side chains are used [48]. Depending upon the route of administration, different hydrogel based dosage forms are designed. The synthesis of hydrogels usually involves crosslinking of polymers within a mould to input the desired shape suitable for administration into body. For various route of administration, different shapes of hydrogels are developed as

i. Personal route- spherical beeds, cylinders and discs [49].
ii. Implants- drum shaped [51], disc shaped [52], cylinder [53],
iii. Rectal routes- cylindrical [54],
iv. Vaginal administration- cylindrical [55], torpedo shaped devices [56].

The function of a hydrogel is based on its properties like equilibrium swelling, swelling kinetics, permeability & biocompatibility [48, 56]. Some characterization parameters are required for efficient product performance and quality assurance of the produced batch.

CHARACTERIZATION PARAMETERS FOR HYDROGELS

Parameter	Techniques of measurement
Network pore size	Quasi-elastic laser light scattering Electron microscopy Mercury porosimetry Rubber elasticity
Crosslinking & Mechanical strength	Ultimate compressive strength Change in polymer solubility with time
Drug distribution	Fourier transform infrared (FTIR) microscopy Scanning electron microscopy (SEM).
Drug diffusion	Membrane permeability Controlled release experiments Nuclear magnetic resonance FTIR spectroscopy Scanning electron microscopy (SEM) Quasi-elastic laser light scattering
Degree of swelling	Volume or mass degree of swelling Equilibrium water content with time

DRUG RELEASE MECHANISM FROM HYDROGEL MATRIXES

In dehydrated state, most of the hydrogels look glassy. Drug release generally involves simultaneous absorption of water & desorption of drug via swelling controlled mechanism. The rate controlling factor mediating drug delivery is the existence of the polymer to an increase in volume and change in shape [57] that is the most common mechanism of drug release from hydrogel matrices is passive diffusion. Focused on the rate limiting step of release phenomena, drug release mechanism from hydrogel can be classified controlled.

- Diffusion controlled
- Swelling controlled
- Chemically controlled.

According to Fick's first law of diffusion (with constant or variable diffusion constants), the diffusion controlled behaviour is most common mechanism to describe drug release from hydrogels [58]. The drug diffusion out of a hydrogel matrix primarily dependent on the mesh sizes within the matrix of the gel [59]. Typical mesh sizes reported for biochemical hydrogels range from 5-100nm [60] which are much larger than most small molecule drugs. In the case of the swelling controlled mechanisms, when diffusion of a drug is faster hydrogel distention, swelling is considered to be controlling for the release behaviour [61, 62].

Controlled release hydrogel systems

Controlled release Drug delivery system should respond to physiological requirement, sense the changes and accordingly alter the drug release profile. The delivery system should be intelligent enough to understand the time of drug release. Thus, drug delivery patterns should be optimized for pulsed or self-regulated mechanism.

STIMULI SENSITIVE HYDROGELS

Hydrogels can exhibit dramatic charges in their swelling behaviour, network structures, permeability or mechanical strength is response to

different stimuli, both external & internal to the body [48]. Responsive hydrogel systems are developed to deliver their contents in response to a fluctuating condition in a way that desirable coincides with the physiological requirements at right time and place. The most considerable drawback of stimuli-sensitive hydrogels is their significantly slow response time, with the easiest way to achieve fast acting responsiveness being to develop thinner & smaller hydrogels, which in term, bring about fragility and loss of mechanical strength in the polymer network and the hydrogel device itself [63].

pH-SENSITIVE HYDROGELS

These hydrogels are prepared from pH sensitive polymers which contains either an acidic or basic pendant group that either accept or release protons in response to environmental pH changes [63]. The swelling of these hydrogels are directly proportional to the changes in case the polymer contains acidic group; whereas are indirectly proportional in case the polymer contains basic group. Their swelling properties due to their ionic networks. The pendent groups in contact with aqueous media of appropriate pH and ionic strength, developed fixed charges on the gel and due to the resulting electrostatic repulsion, the solvent uptake in the network is increased [25].

TEMPERATURE SENSITIVE HYDROGELS

These are prepared from polymers which shows sensitivity to temperature. Relating to the surrounding temperature these hydrogels can swell as well as contract. Temperature sensitive hydrogel are classified into –positively thermosensitive, negatively thermosensitive and thermos reversible gel [25]. The swelling property of hydrogels depends on the critical solution temperature (CST). In case of positive thermosensitive hydrogel, they have Upper Critical Solution Temperature (UCST) and it contracts upon cooling below the UCST. Polymers used in positive thermosensitive hydrogel and poly-acrylic acid (PAA), poly-acrylamide (PAAm).In case of negative thermosensitive hydrogel, they have Lower Critical Solution Temperature (LCST). Copolymers of N-isopropylacrylamide (PNIAAm) are usually used for these. The most commonly used thermoreversible hydrogel are prepared from poly (ethylene oxide)-b-poly (propylene oxide)-b-poly (ethylene oxide). Examples- Pluronics, Tetronics, Poloxamer [25].

HYDROGELS FOR PHARMACEUTICAL APPLICATION

Hydrogels have been attempted extensively to achieve ideal drug delivery systems with desirable therapeutic features [61]. Pharmaceutical hydrogels have been categorized on the basis of different criteria which includes route of administration, type of material being delivered, release kinetic etc. Pharmaceutical hydrogels can be classified as [25]

- Oral hydrogel system
- Topical and Transdermal hydrogel systems
- Hydrogel device for gastro-intestinal drug delivery
- Hydrogel based on ocular delivery systems
- Hydrogels based on rectal & vaginal delivery system

Oral route can deliver drugs to four major specific sites – mouth, stomach, small intestine and colon [25].

BIOMEDICAL APPLICATION OF HYDROGELS

Polymeric hydrogels that are biocompatible and bio-degradable are widely used for designing.
Different drug delivery systems in

- Pulsatile Drug delivery,
- Insulin protective and control of its delivery by glucose,
- Contact lens based ophthalmic system,
- Tissue engineering & regenerative medicine,
- For protein and drug release.

Ionic hydrogels find more wide application in pharmaceutical products over the neutral networks in drug delivery. The high water retaining capacity of the hydrogels makes them more biocompatible and thus they also find application in designing contact lenses, membranes for biosensors, linings for artificial hearts, material for artificial skin and other drug delivery devices [27]. The use of hydrogel matrix for drug delivery involves the dispension of the drug in the matrix followed by drying of the system and concomitant immobilization of the drug [64].

TABLE-1: ROUTE OF ADMINISTRATION OF HYDROGELS

Route Of Administration	Shape	Example	References
Parenteral	–	Regel® (PLGA-PEG-PLGA) was used as a drug delivery carrier for the continuous release of human insulin and steady secretion of insulin was achieved for 15 days.	[67]
Ocular	Contact lenses, Drops, Suspensions, Ointments, Circular inserts	Formulation containing Carbapol® 940 and Methocel ESOLV (HMPC) is used for sustained release of ofloxacin over an 8 hour period.	[68]
Peroral	Spherical beds, Discs, Nanoparticles	Hydrogel made up of varying proportion of PAA derivative and crosslinked PEG allowed preparing silicone microsphere, which release prednisolone in the GIT.	[69]
Rectal	Suppositories	With Xyloglucan gel, a more sustained release of indomethacin was achieved invitro in comparison with commercial suppositories.	[70]
Topical	Dressings	BSA-PEG hydrogels are partially applied as controlled release devices in wound dressings.	[70]

TABLE-2: MARKETED PRODUCTS OF HYDROGELS

Sl. No	Product	Hydrogel composition	Indication	Remarks	Manufactured or marketed by	References
1.	Smart Hydrogel™	Poly(acrylic acid) and poly (oxypropylene- co-oxyethylene) glycol	Used for development of ophthalmic, buccal nasal, vaginal, transdermal, injectable and implantable	Mucoadhesive liquid composition that undergoes sol–gel transformation at body temperature, can be tailored for stimuli responsive drug delivery	MedLogic Global (Plymouth, UK)	http://www.medlogic.com
2.	Moraxe™	--	End-stage cancer pain	Once-daily rectal slow-release product of morphine sulfate	CeNeS Pharmaceuticals; marketed by Schwartz Pharma	http://www.cenes.com
3.	Cervidil® vaginal insert	Poly(ethylene oxide) and urethane	Initiation and/or continuation of cervical ripening at or near term	Product contains 10 mg dinoprostone (PGE2) and exhibits *in vivo* release rate of ~0.3 mg h^{-1}	Controlled Therapeutics, UK; marketed by Forest Pharmaceuticals (St Louis, MO, USA)	http://www.btgplc.com
4.	SQZ™ Oral controlled release system	Chitosan and polyethylene glycol	Hypertension	pH-Sensitive, once- a-day tablet of diltiazem hydrochloride	Macromed (Sandy UT, USA)	http://www.macromed.com
5.	Hycore-V™ and Hycore-R™	--	Vaginal and rectal infections, respectively	Localized delivery of metronidazole	CeNeS Drug Delivery (Irvine, UK)	http://www.cenes.com
6.	Aquamere™	Interpolymers of PVPand PVP- -grafted copolymers with urethane	Skincare, topical and oral drug delivery	--	Hydromer (Somerville, NJ, USA)	http://www.hydromer.com
7.	Aquatri™ II	Chitosan–PVP	Skin adhesive gels, wound and burn dressings, implants, and drug delivery matrices	--	Hydromer	http://www.hydromer.com
8.	Hypan®	Hydrophilic acrylate derivatives with a unique	Used in the manufacture of soft contact lenses, and moisturizing	--	Hymedix International (Dayton, NJ, USA)	http://www.hymedix.com

		multiblock structure	wound gels and dressings			

CONCLUSION

In modern era, the invention of hydrogels is definitely a good step for pharmaceutical formulation. With increasing efforts devoted to controlled release of drug molecules, the application of hydrogels will continue to grow in future with its more relevantly and more efficiently applications. The success of hydrogels as delivery systems can be judged by several marketed preparations. At present, the major considerations during the formulation of hydrogel-based drug products are their mechanical strength and response-time in a physiological environment. Fast-responding hydrogels releasing maximal drug in less time while maintaining the structural integrity in a biological system will be the more appreciated delivery systems. Moreover, the application of hydrogel will be immense in the coming future owing to its excellent biocompatibility and similarity to the bio-membrane.

ABBREVIATIONS

HA- Hyaluronic acid; PEG-Poly ethylene glycol; PLA-Poly lactic acid; PLGA-Poly lactic-co-glycolic acid; PCL-Poly caprolactone; PHB-Poly hydroxy Butyrate; PF-Propylene fumarate; EG-Ethylene glycol; PBO-Poly butylene oxide; CD-Cyclodextrin; PAAm-Polyacrylamide; PNIPAAm-Poly N-isopropyl acrylamide; PVA-Poly vinyl alcohol; PVamine-Poly vinyl amine PVAc-Poly vinyl acetate; PNVP-Poly N-vinyl pyrrolidone; PAAc-Poly. Acrylic acid; HEMA-Hydroxyethyl methacrylate; PAN-Polyacrylonitrile; PGEMA-Poly glucosylethyl methacrylate; PEO-Poly ethylene oxide; PPO-Poly propyleneoxide; PHPMA-Poly hydroxypropyl methacrylamide; PEMA-Poly Ethyl methacrylate; PAN-Polyacrylonitrile; PMMA-Poly methyl methacrylate.

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