Review Article

TIPS Trends in Pharmaceutical Sciences 2019: 5(1): 7-24.

Hydrogels as Drug Delivery Systems; Pros and Cons

Parisa Ghasemiyeh[1,2], Soliman Mohammadi-Samani[2,3]

[1]Department of Clinical Pharmacy, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran.
[2]Department of Pharmaceutics, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran.
[3]Center for Nanotechnology in Drug delivery, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran.

Abstract

Hydrogels are cross-linked polymers with hydrophilic groups which enable them to absorb large amounts of water. Although hydrogels have numerous capability and advantages in drug delivery including biocompatibility, low toxicity and good swelling behavior but depending on chemical moieties of the gel forming polymers and route of administration some limitations would appear in delivery of active pharmaceutical using hydrogel as delivery vehicle. In this review at first classification of the hydrogel with different approaches including chemical moieties, crosslinking agent behaviors and release controller mechanism was performed and limitations arise from each category was described and finally different approaches to overcome each of this limitation was proposed.

Keywords: Drug delivery, Hydrogels, Polymers, Pros and Cons.

1. Introduction

Hydrogels are novel drug delivery systems which have been considered since the early 1960s. First of all Wichterle and Lim introduced a kind of hydrophobic gel, cross-linked hydroxyethyl methacrylate (HEMA) hydrogels, developed for biological purposes (1, 2). Hydrogels have many advantages such as their biocompatibility potential, hydrophilicity, controlled drug release and smart drug delivery, etc. (3). So, there was a great interest among scientists of different fields to develop and progress these delivery systems. Hydrogels are hydrophilic polymers with cross-links which form a polymeric network enable them to absorb water from 10-20 percent up to thousands times of their own weight (2, 4). There are two kinds of hydrogels; chemically cross-linked or permanent hydrogels, which are stable to degradation during swelling, and physically cross-linked or reversible hydrogels, which degrade and dissolve during water absorption (1, 2). In chemically cross-linked hydrogels, polymers are cross-linked with covalent bonds (5), but in physically cross-linked hydrogels, polymers are bond together with hydrogen bonds, ionic bonds or hydrophobic bonds (6). The ability of water absorption and swelling of hydrogels results in the presence of hydrophilic moieties in their polymeric structure but their resistance in water dissolution is the outcome of the presence of cross-linkers between the polymeric chains (7). Polymers which are used in hydrogel preparation would be from natural or synthetic sources, each of these types of polymers could have pros and cons and they should be selected according to hydrogels application and target site of drug delivery.

Corresponding Author: Soliman Mohammadi-Samani, Department of Pharmaceutics, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran.
Email: smsamani@sums.ac.ir

2. Hydrogels classification

Hydrogels may be classified based on their sources (natural or synthetic hydrogel), their

Recieved: 27/01/2019; Accepted: 28/02/2019

polymeric compositions (homo-polymer, co-polymer and multi-polymer hydrogels), physical structure (amorphous, semi-crystalline and crystalline hydrogels), cross-linkers (physical and chemical cross-linked hydrogels), electrical charge (non-ionic, cationic, anionic, amphoteric and zwitterionic hydrogels) and release controllers (time-controlled hydrogels and stimuli-induced or smart hydrogels) (1, 7). (Figure 1)

3. Release mechanisms

3.1. Diffusion-controlled

Diffusion-controlled release is the most common mechanism of drug release from hydrogels. In this type of drug release, Fick's diffusion theory is used for kinetic modeling (8-11). For porous hydrogels with pore sizes of larger than drug molecule dimensions, drug diffusion from hydrogels could be related to the porosity and also the tortuosity of hydrogels. Diffusion-controlled release hydrogels might be act as reservoir or matrix. In reservoir drug delivery systems, drug molecules are encapsulated and surrounded by polymeric hydrogels and so drug release mostly obeys the first law of Fickian diffusion (8). In matrix drug delivery systems, drug molecules are homogenously dispersed in polymeric hydrogels and drug release mostly follows the second law of Fickian diffusion.

3.2. Swelling-controlled

Swelling-controlled drug release could occur when the rate of dug diffusion is faster than the rate of hydrogel swelling. For purely swelling-controlled drug release, the kinetic model of release could be mostly fit to zero-order model (8, 11). Hydrogels may have swelling-induced transition phase (at glass transition temperature or Tg) from glassy to rubbery state which causes faster drug diffusion and release from polymeric chains. In swelling-controlled delivery systems, the higher the rate of hydrogel swelling, the higher the rate of drug release, so the rate and ability of hydrogels' water absorption and the thickness of polymeric gels are important factors in swelling-controlled delivery systems (8, 12, 13).

3.3. Chemically-controlled

Chemically-controlled drug release mechanism explains the mechanism in which a reaction occurs within the hydrogel matrix. In these reactions enzymatic or hydrolytic cleavage of polymeric network is responsible for drug release. Drug release in chemically-controlled delivery systems could be occured by cleavage of polymeric chains through bulk or surface erosion and following these mechanisms, the entrapped drug or tethered drug would be released from hydrogels (8, 10, 11, 14). The polymer chain cleavage is the rate-limiting step of chemically-controlled

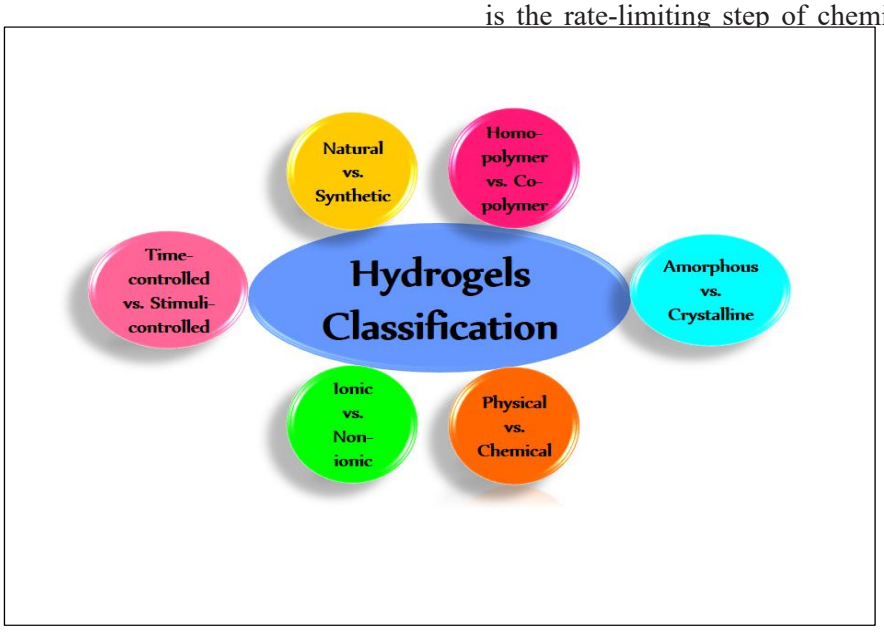

Figure 1. Hydrogels classification.

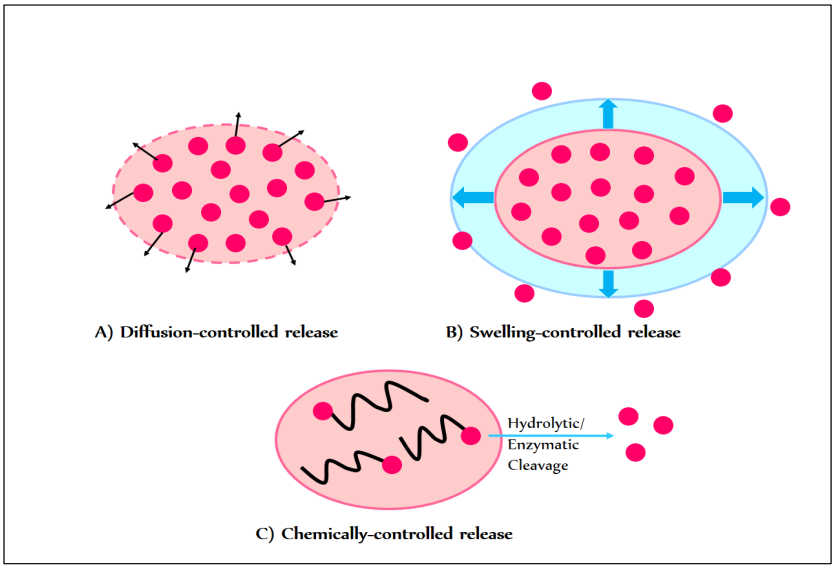

Figure 2. Schematic view of drug release mechanisms from hydrogels; A) diffusion-controlled release, B) swelling-controlled release, and C) chemically-controlled release.

release systems and in this system, drug molecular diffusion has no significant effect on drug release (Figure 2).

4. Structure of hydrogels

Hydrogels could be prepared from natural or synthetic polymers. The monomers which are used in hydrogel preparation would be hydrophilic or hydrophobic. Generally, any method used to cross-link the polymers, could be used in hydrogel preparation. Polymers might be cross-linked through chemical or physical reactions or through ionizing radiation method (7). The most important ingredients in hydrogel preparation are monomers, cross-linkers and initiators. According to types of preparation, hydrogels are categorized as the following (Figure 3):

4.1. Homo-polymeric network

Homo-polymeric networks are formed from a single type of monomers. According to the nature of monomers and the polymerization technique, it would be possible for homo-polymers to have cross-linked structures (7).

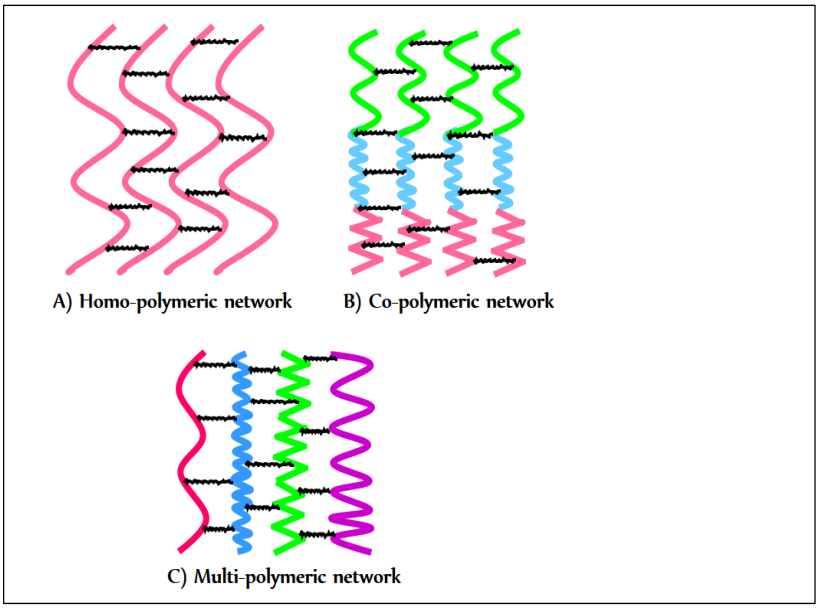

Figure 3. Schematic view of hydrogels categories according to methods of preparation; A) homo-polymeric network hydrogels, B) co-polymeric network, and C) multi-polymeric network hydrogels.

4.2. Co-polymeric network

Co-polymeric hydrogels are formed from two or more than two types of monomers. In these hydrogels, the presence of one or more hydrophilic component is necessary (7). The hydrophilic moiety in copolymers is necessary to obtain the swelling ability of hydrogels (15).

4.3. Multi-polymeric network

Multi-polymeric hydrogels are formed from two independent cross-linked polymers (7). These dual polymers have amazing properties superior than each of the single polymers. Multi-polymeric hydrogels are developed to interpenetrating (IPN) hydrogels which are the combination of two polymers in a network and at least one of these polymers is cross-linked or synthesized (15).

5. Polymers used in hydrogel preparation

5.1. Natural polymers

Natural polymers usually have the advantage of biocompatibility and biodegradability, but because of the distress of purification, their most common limitation is batch to batch variation which causes differences in final formulation (16). Some of the most important natural polymers which are used in hydrogel preparation are listed in the following section.

5.1.1. Chitosan

Chitosan is a well-known natural polymer and has many advantages in drug delivery systems such as mucoadhesive and bioadhesive properties, absorption-enhancing properties and controlled drug release (16). Chitosan is a water soluble (in light acidic pH) and cationic (positive charge) polymer. The most important advantages of this polymer are its biocompatibility and low toxicity potential (1). Chitosan also has some limitations such as small specific surface area and void fraction that should be overcome (17).

5.1.2. Hyaluronic acid

Hyaluronic acid is a mucopolysacharide which is naturally existing in cartilage and connective tissue. Hyaluronic acid has a poly-anionic nature and so it could be cross-linked to cationic polymers. Hyaluronic acid could be degraded by hyaluronidase (18). Hyaluronic acid is a suitable choice in local delivery because of its biocompatible and biodegradable nature and visco-elastic and unique rheological properties. It could induce cell mobility and cell proliferation and also cause wound healing. Hyaluronic acid is used in hydrogel preparation and has the advantage of delayed drug release and prolonged duration of action (19).

5.1.3. Carrageenan

Carrageenan is a natural polysaccharide and because of its gelation capability has the advantage of controlled drug release. Carrageenan is an anionic, biocompatible and low toxic polymer. It seems that κ-carrageenan is the most suitable form of carrageenan for drug delivery and tissue engineering purposes (20).

5.1.4. Alginic acid

Alginic acid is an anionic polysaccharide which is highly water soluble and has the gelation capability. It has the advantage of biocompatibility and low toxicity (1). Alginic acid could instantly form a gel in combination with calcium ions (21) and could be used as drug carrier.

5.1.5. Collagen

Collagen is a biocompatible and biodegradable polymer which is widely used in pharmaceutical industries (22). It is a very suitable choice for implant preparation. Collagen could control drug release from hydrogels and also could induce cell growth (23). Collagen would be widely used as a scaffold for tissue engineering purposes.

5.2. Synthetic polymers

5.2.1. Poly ethylene glycol (PEG)

Polyethylene glycol is a synthetic and bio-functional polymer. PEG has the advantage of biocompatibility and adaptable physical properties. PEG is capable to form controlled gelation responsive to a photo-initiator or by mixing it with cross-linkers (24). PEG hydrogels have degradable (hydrolysable) moieties in their structures.

5.2.2. Poly lactic acid (PLA)

Poly lactic acid is a synthetic, biodegrad-

able, biocompatible and hydrophobic polymer. PLA has the limitation of dispersing hydrophilic materials in their polymeric structures and uncontrolled drug release pattern. These problems could be solved by cross-linking PLA to hydrophilic PEG polymers which is strongly hydrated and capable to sustain and prolong drug release. PEG/PLA copolymerization has the advantage of both hydrophilic and biodegradable polymers. PEG grafting to PLA induces hydrophilicity in the polymer and PLA fraction of the molecule induces the biodegradability on it (25).

5.2.3. Poly lactic co-glycolic acid (PLGA)

PLGA is a biocompatible, biodegradable polymer with suitable mechanical characteristics. PLGA could be used in drug delivery systems because of the advantage of sustained and prolonged drug release (26). Although PLGA is a biodegradable polymer, but micro environmental acidity following polymer degradation, could induce irritation at the site of formulation application and could also damage peptide/protein drugs which are loaded to hydrogels (16).

5.2.4. Poly vinyl alcohol (PVA)

PVA is a biodegradable, biocompatible, hydrophilic and synthetic polymer. PVA would be widely used in tissue engineering to repair damaged organs or tissues. Using the optimal PVA to water ratio could produce a suitable hydrogel which could simulate natural tissues properties (27).

5.2.5. Poly caprolactone (PCL)

PCL is a biocompatible, biodegradable and hydrophobic synthetic polyester which is highly used in drug delivery and tissue engineering (28). PCL has the advantage of adoptability to physical, mechanical and chemical changes because of the ease and potential of its co-polymerization with other polymers. PCL is compatible with both natural and synthetic polymers. Because of the hydrophobic nature, lipophilic drugs could be homogenously dispersed in polymeric matrix, but hydrophilic drugs mostly migrate to the surface of PCL polymers (29).

5.3. Semisynthetic polymers (Cellulose derivatives)

5.3.1. Carboxymethyl cellulose (CMC)

CMC is a biocompatible and biodegradable polymer which is widely used for biomedical purposes. CMC is a water-soluble derivative of cellulose (ether of cellulose) and is now available in market with low cost and high purity (30). CMC could be easily cross-linked to produce hydrogels.

5.3.2. Hydroxyethyl cellulose (HEC)

HEC is a water soluble and biocompatible derivative of cellulose. HEC has many OH groups in its structure and has the advantage of being modified and improved by grafting polymerization with vinyl groups (31). HEC has better swelling properties when cross-linked with CMC and forms novel hydrogels. The water absorption and swelling ability of these hydrogels could be optimized by adjusting suitable HEC/CMC ratio and amount of cross-linkers used in hydrogel preparation (32).

5.3.3. Methyl cellulose (MC)

MC is a semi-flexible linear derivative of cellulose and some of the hydroxyl groups are substituted with methoxy groups. The ratio of hydroxyl to methoxy groups could prescribe the water solubility of this polymer. The gelation of MC could be occurred at sol-gel transition temperature (Tg) by nucleation and growth mechanism (33).

5.3.4. Hydroxypropyl cellulose (HPC)

HPC is a highly water soluble derivative of cellulose. HPC hydrogels are usually used in dye removal of aqueous solutions. The most important limitation of HPC hydrogels is their low capacity of water absorption which could be overcome by incorporation of nano-fillers with large specific surface area within these hydrogels (34).

5.3.5. Hydroxypropyl methyl cellulose (HPMC)

HPMC is a water soluble derivative of cellulose which is widely used in controlled drug delivery systems. The most important characteristic of HPMC is the high swelling capability that could control the release of incorporated active pharmaceutical ingredient. Physicochemical properties of HPMC polymers could be described according to

the molecular weight, methoxy substitute content and hydroxypropoxy substitute content in their structures (13).

6. Hydrogel applications and different routes of administration

Hydrogels could be used as drug delivery systems through different routes of administration as listed in Table 1.

6.1. Oral route

Oral drug delivery is the most common and desirable route of drug administration and has the best patient compliance. Co-polymer hydrogel networks act as a suitable carrier for oral drug delivery, since they can improve oral absorption and bioavailability. Hydrogels are considered as safe drug delivery system for oral route of administration and also have the muco-adhesive capability which could prolong drug release and absorption. The other advantage of hydrogels as oral drug delivery systems is the ability of the protection of incorporated drug from enzymatic degradation (35). Hydrogels are mostly studied in oral drug delivery

Table 1. Different loaded drugs and routes of administration of hydrogels.

	Route of Administration	Loaded Drug	First Author	The major goal of the study	Ref.
1	Oral	-	Paolo Colombo	Study the use of hydrogel matrices or swelling-controlled delivery systems for oral drug delivery.	(46)
		-	Kim Knuth	Study the use of hydrogels for drug delivery to the vaginal and oral areas (oral cavity, stomach, small, intestine, colon and rectum).	(47)
		Flavin mononucleotide	Waleed S.W. Shalaby	Using enzyme-digestible hydrogels for once daily oral drug delivery by long-term gastric retention potential.	(48)
		Insulin	Mariko Morishita	Using cross-linked polymer microparticles for oral insulin delivery.	(35)
		Insulin	Kiran Chaturvedi	Study the use of hydrogel-based devices for oral insulin delivery.	(36)
		Insulin	Bumsang Kim	Using photopolymerized pH-responsive hydrogels for oral insulin delivery with the potential of protective effect and change in insulin release rate.	(49)
		Chlorhexidine gluconate	S. S¸ enel	Using chlorhexidine incorporated in chitosan hydrogel for oral candidiasis.	(50)
2	Parenteral	Tyramine	K.S. Kim	Using injectable radical cross-linked hyaluronic acid–tyramine hydrogels in rheumatoid arthritis.	(51)
		rTIMP-3	Brendan P. Purcell	Using bio-responsive injectable hydrogels for the purpose of as-needed matrix metalloproteinase inhibition to prevent different pathologies.	(52)
		-	Amit Alexander	Study the use of thermosensitive injectable hydrogels for biomedical applications.	(37)
		Tramadol	Lorina Bisharat	Study the release of tramadol from Poloxamer thermo-sensitive hydrogels.	(53)
		Insulin	Sabrine S. Jensen	Evaluating the release of insulin implants in a hydrogel matrix.	(54)
		Peptide and protein	Mayura Oak	Study the use of “smart hydrogels” for controlled parenteral peptide and protein delivery.	(55)
		Protein	Tina Vermonden	Study the use of hydrogels for protein delivery.	(56)

Continued Table 1.

	Route of Administration	Loaded Drug	First Author	The major goal of the study	Ref.
3	Nasal	-	Jie Wu	Using PEG and chitosan-based thermosensitive hydrogels for nasal drug delivery.	(57)
		-	H. Nazar	Using N-trimethyl chitosan-based thermosensitive hydrogel for nasal drug delivery.	(38)
		-	Barbara Luppi	Study the use of chitosan-based hydrogels for nasal drug delivery.	(58)
		-	Xiaofeng Xu	Using poloxamer and Ɛ-poly lysine-based thermosensitive and mucoadhesive hydrogels for nasal drug delivery.	(59)
		Phenylephrine hydrochloride	Ibrahim A. Alsarra	Using poly(vinylpyrrolidone) hydrogels for nasal mucosal drug delivery.	(60)
		Acyclovir	Ibrahim A. Alsarra	Using mucoadhesive poly(vinylpyrrolidone) hydrogels for nasal delivery of acyclovir.	(61)
		Antipsychotic drug	Barbara Luppi	Using chitosan/pectin based hydrogel nasal inserts to improve the bioavailability of antipsychotic agents.	(62)
4	Ocular	-	M. Zignani	Study the use of semi-solid ophthalmic viscose and mucoadhesive hydrogels to improve ocular residence time and drug bioavailability.	(63)
		-	Derya Gulsen	Preparation of a dispersion of microemulsions drops in poly-2-hydroxyethyl methacrylate (p-HEMA) hydrogels for the purpose of ocular drug delivery.	(39)
		Acetazolamide	Andreza Ribeiro	Using HEMA polymer as a backbone component with the potential of cytocompatible and biomimetic properties for controlled ocular drug delivery.	(64)
		-	Li Xinming	Study the use of polymeric hydrogels for ocular drug delivery through contact lens.	(65)
		-	Eugen Barbu	Preparation of nanoparticulate hybrid polymeric hydrogels with both thermosensitive and swelling properties for ocular drug delivery.	(66)
		-	Xiaohong Hu	Study the use of hydrogel contact lens for the purpose of controlled ocular drug delivery.	(40)
		-	HongBo Yin	Synthesis of a biodegradable and thermosensitive poly(ethylene glycol)-poly(e-caprolactone)-poly-(ethylene glycol) (PEG-PCL-PEG) (PECE) triblock copolymer in situ hydrogel for sustained ocular drug delivery.	(67)
5	Topical	Betamethasone-17-valerate	Taner S¸ enyi˘git	Using topical deoxycholate hydrogels of betamethasone-17-valerate in order to avoid skin irritation.	(68)
		-	Claudia Valenta	Study the use of Deoxycholate-hydrogels as novel topical drug delivery systems.	(69)

Continued Table 1.

	Route of Administration	Loaded Drug	First Author	The major goal of the study	Ref.
		Propranolol hydrochloride	T. Cerchiara	Formation of physically cross-linked chitosan hydrogels with lauric, myristic, palmitic or stearic acid for topical delivery of hydrophilic agents.	(70)
		Silver sulfadiazine	Nadia M. Morsi	Using Silver sulfadiazine based cubosome hydrogels (cubogels) in order to treat deep second degree burns.	(41)
		Econazole nitrate	Vanna Sanna	Preparation of solid lipid nanoparticles incorporated to HPMC hydrogels for topical delivery of econazole nitrate.	(71)
		Nonivamide	Jia-You Fang	Using chitosan and carboxymethylcellulose hydrogels of nonivamide to improve skin permeation and distribution.	(72)
		Isosorbide mononitrate	Yoncheva, Krassimira	Using Carbopol 940-based hydrogels for topical delivery of isosorbide mononitrate for the treatment of fissures.	(73)
		-	Diarmaid J. Murphy	Evaluation of the efficay of poly(vinyl alcohol) tetrahydroxyborate hydrogels as topical drug delivery systems.	(74)
		Terbinafine hydrochloride	İpek Özcan	Using low molecular weight chitosan hydrogels to improve topical delivery of terbinafine.	(75)
6	Brain delivery	Peptide or aminosugar	Giles W. Plant	Evaluation of the use of synthetic hydrogels containing the sequence of arginine–glycine–aspartic acid (RGD) peptide and aminosugars, which are found in many Extracellular matrix glycoproteins.	(76)
		-	K. B. Bjugstad	Using PEG-based hydrogels implants to provide tissue engineering and sustained drug release in central nervous system (localized recruitment and activation of microglia and astrocytes).	(77)
		-	Lina Ratiba Nih	Study the use of hydrogel scaffolds for brain repair after stroke.	(78)
		Erythropoietin	Yuanfei Wang	Using hyaluronan/methyl cellulose (HAMC) hydrogels for erythropoietin delivery to the brain in order to endogenous stem cell stimulation after stroke.	(42)
		Paclitaxel	Sudhir Hulikal Ranganath	Fabrication of paclitaxel-loaded PLGA microspheres in order to achieve implantable sustained release glioma chemotherapy.	(79)
		Cyclosporine A	Matthew J. Caicco	Using parenteral PLGA/HAMC composite for sustained brain delivery of cyclosporine A to treat stroke.	(80)
		Curcumin	Xi Chen	Preparation of a Poloxamer 188-based thermosensitive hydrogel to enhance brain targeted delivery of curcumin.	(81)
7	Tissue engineering	Bone, muscle, and blood vessels	Kuen Yong Lee	Guiding tissue formation in mechanically stressed environments by hydrogels.	(82)
		Different tissues	Jeanie L. Drury	Guiding tissue formation in mechanically stressed environments by hydrogels.	(83)

Continued Table 1.

	Route of Administration	Loaded Drug	First Author	The major goal of the study	Ref.
		Cartilage tissue	Nguyen, Kytai Truong	The use of photopolymerizable hydrogels in tissue engineering.	(84)
		Vascular tissue	Ali Khademhosseini	The use of microengineered hydrogels for tissue engineering.	(44)
		Soft tissues	Junmin Zhu	The use of bioactive polyethylene glycol hydrogels as tissue engineering scaffolds.	(85)
		Damaged tissue	S. Sayyar	The use of chitosan/graphene composite hydrogels for tissue engineering	(86)
		adipose, bone, cartilage, intervertebral discs and muscle tissue	A. Sivashanmugan	The application of injectable hydrogels in tissue engineering.	(43)
		Vascular, muscular, and neural tissues	Jeroen Leijten	Study of the spatiotemporal control over biomaterials for tissue engineering purposes.	(87)
		Dermal, heart valve, vascular, corneal and esophageal tissue	Sheva Naahidi	Design of non-invasive, biocompatible, and smart hydrogels for tissue engineering purposes.	(88)
8	Gene delivery	GFP expressing plasmid	Mariam Mohammadi	Synthesis of folic acid coupled poly(L-lactide)-b-poly(ethylene glycol) and three-layered micelles for gene delivery to activate macrophages in rheumatoid arthritis treatment.	(89)
		Vascular endothelial growth factor-165 (VEGF) pro-angiogenic gene	Arghya Paul	Preparation of injectable and biocompatible methacrylated gelatin hydrogel to deliver polyethylenimine functionalized graphene oxide nanosheets complexed with DNAVEGF to promote vacuologenesis and cardiac repair for myocardial therapy.	(90)
		Anti-oncogene	Yi Yang	Preparation of a biodegradable folate-poly(ester amine) polymer and a PECE thermosensitive hydrogel composite for sustained gene delivery to increase anti-tumor effect.	(91)
		Non-viral vectors	Jeremy Zhang	Using poloxamin/fibrin hybrid hydrogels to induce localized and controlled non-viral gene delivery.	(92)
		Calcium phosphate-DNA	Melissa D. Krebs	Using injectable alginate hydrogels for gene delivery of calcium phosphate DNA nanoparticles in order to promote osteogenesis.	(93)

Continued Table 1.

Route of Administration	Loaded Drug	First Author	The major goal of the study	Ref.
	VEGF and βgal	Yuguo Lei	Synthesis of poly ethylene imine /DNA polyplexes (by caged nanoparticle encapsulation (CnE) technique) into hyaluronic acid and fibrin hydrogels for local gene delivery purposes.	(45)

of insulin to overcome the complications associated with parenteral insulin administration (36).

6.2. Parenteral route

For many drugs such as peptide and protein, parenteral route is the most favorite route of administration. Hydrogels as controlled drug delivery systems could be used for parenteral drug delivery. Hydrogels can be used to prolong and sustain drug release, increase drug half-life, increase bioavailability, drug protection against enzymatic degradation, decrease frequency of drug administration and so increase patient compliance. Injectable hydrogels are usually temperature sensitive so they are sol (fluid) at room temperature and gel (viscous) at body temperature. The gelation process is able to sustain drug release and improve drug bioavailability. Poloxamer-based hydrogels are the most common temperature sensitive hydrogels which were used in parenteral drug delivery systems, but their limitation is the lack of biodegradability (37).

6.3. Nasal route

Nasal drug delivery has the advantages of high patient compliance and prevention of hepatic first pass effect which could increase drug bioavailability. However, this route of delivery also has its own limitation including barrier action to the absorption of the macromolecules across the mucosal membranes and short nasal residence time because of mucosal turnover. Hydrogels with mucoadhesive, viscoelastic and biocompatible properties (such as chitosan hydrogels) are highly considered as novel carriers for nasal delivery which could increase nasal residence time of loaded active ingredients. Most of the polymers used in nasal delivery systems are thermosensitive and capable to form gel at site of action at body temperature (38).

6.4. Ocular route

Ocular drug delivery via eye drops is a common route of topical administration which is not efficient enough and may cause systemic adverse reactions. Only about 5 % of the incorporated drug could reach to the intraocular tissue, but about 95 % would be lost through tear drainage. Also, the residence time of drug in the eye is very short. So, the development of novel drug delivery systems to increase drug residence time and decrease drug loss and systemic adverse effect, would be highly desirable (39). Many researchers considered contact lenses as ocular drug delivery systems which have the advantage of increasing drug residence time and drug bioavailability. Hydrogel contact lenses because of their transparency and biocompatibility were widely considered as ocular drug delivery systems. In this regard drug molecules could be homogenously dispersed in hydrogel matrices (such as HEMA polymers), but this method is only limited to hydrophilic drugs and may cause fast drug release (39). In order to solve this problem, hydrophobic or ionic monomers could be incorporated to HEMA hydrogels to increase drug-hydrogel interaction and control drug release rate and also could increase drug loading capacity (40).

6.5. Topical route

Topical drug delivery is one of the favorite routes of administration which is used to reduce adverse effects and to localize high amounts of drug at target site. Hydrogels because of the low toxicity potential and sustained drug release are considered as suitable carriers for topical drug delivery. Also, hydrogels have the advantage of biocompatibility, softness and high water content which could mimic natural tissues properties and because of their swelling and hydrating capabil-

ity, could avoid irritation to enclosed tissues. The other important advantage of hydrogels is the ability of drug protection against harsh environmental conditions (41).

6.6. Brain delivery

Drug delivery to brain is still associated with so many challenges and the most important problem is the presence of blood brain barrier. Using implants within the brain could be used for local drug delivery, but have the disadvantage of brain tissue damage and infection. Another approach for brain local delivery is epi-cortical delivery using hydrogels which could release the loaded drug directly to the brain with negligible tissue damage (42).

6.7. Tissue engineering

Hydrogels have many advantages for tissue engineering purposes such as similarity to the extracellular matrices of tissues, induction of cell proliferation, negligible irritation to adjacent tissues and sustained release of incorporated growth factors. Injectable hydrogels have superiorities in comparison to other conventional scaffolds (preformed hydrogels) like the ease of handling, deeper penetration to tissues, better margin adaptation and less invasiveness (43). Micro-engineered hydrogels are other promising engineering tools to overcome current challenges facing tissue engineering (44).

6.8. Gene delivery

Gene delivery through hydrogel scaffold is delivery of DNA or RNA for the purpose of genetic modification. Hydrogels are capable to increase gene therapy efficacy especially in cancer therapy. In cancer therapy, siRNA or the lethal genes would be encapsulated within hydrogel scaffolds and promote apoptosis of cancerous cells. Gene delivery through hydrogels also have some limitations such as limited gene loading capacity and rapid expulsion of encapsulated genes. Several methods have been considered to overcome these limitations like the condensation of DNA or RNA in nanoparticulate systems and then encapsulate them in a hydrogel scaffold (45).

7. Hydrogel limitations and possible approaches for each limitation

During this study numerous papers dealing with hydrogel based drug delivery systems were reviewed to address different limitations of hydrogels. Various approaches for each group of these limitations are summarized in Table 2.

8. Conclusion

Although hydrogel with different chemical

Table 2. Most common limitations of hydrogels as drug delivery systems and possible approaches.

	Limitations	Solutions
1	Non-biocompatible and non-biodegradable properties of some hydrogels	● Development of biocompatible and biodegradable hydrogels including PEG-PLGA-PEGa or using polymers that have hydrolysable moieties (chemical modification) (94).
2	Too slow responsiveness of stimuli-sensitive hydrogels	● Making thinner and smaller hydrogels which are fast-acting (3).
3	A rapid burst drug release during hydrogel swelling and fast drug release from large porous hydrogels	● Covalently or physically linking of the drug to the polymer chains prior to gelation (tethering method) (95). ● Preparation of di-block or tri-block copolymers by covalent cross linking method to overcome rapid dissolution and fast drug release (96).
4	Possibility of drug deactivation and initial burst release in entrapment method	● Application of tethering method (95).
5	Possibility of drug deactivation during polymer binding in covalent binding method	● Using appropriate linkers, in which drug release could be tuned, instead of direct covalent binding of drug to polymer.

Continued Table 2.

	Limitations	Solutions
6	Non-specific drug release mechanism in diffusion-controlled release hydrogels	● Using chemically and biologically stimulated release triggers to control the drug release from hydrogels (95).
7	Potential toxicity of residual unreacted small-molecule cross-linkers in small molecule cross-linking method for hydrogel making	● Using polymer-polymer cross-linking method by formation of Schiff base or Michael addition reaction (96).
8	Limited hydrophobic drug delivery via hydrogels and non-homogenous dispersion of hydrophobic drugs within hydrogels	● Introducing hydrophobic domains directly into the hydrogel network. ● Formation of a solid molecular dispersion of poorly soluble drug. ● Encapsulation of drug in polymer nanoparticles to obtain well-dispersed drug slurry. ● Preparation of a novel nanoparticle and hydrogel composite drug delivery system (96, 97). ● Preparation of lipid-based nanoparticles (solid lipid nanoparticles and nanostructured lipid carriers) as suitable nanocarriers for hydrophobic drugs (98-100) and then incorporate them in hydrogels.
9	Difficulty of incorporation of drug-loaded colloidal carriers in hydrogels	● Preparation of mixed delivery systems such as Liposome-in-hydrogels (101).
10	Fast dissolution of chitosan-based hydrogel matrices in stomach acidic pH for oral drug delivery systems	● The formation of poly electrolyte complexes, conjugation or cross-linking ● Nanoparticle synthesis such as chitosan-poly (g-glycolic acid) based hydrogels for oral insulin delivery (36).
11	Lack of biodegradability and toxicity potential of Poloxamer-based thermosensitive hydrogels	● Preparation of PEG-based hydrogels which are cross-linked to hydrophobic polyesters such as PLGA and PCLb which are biodegradable and biocompatible (102). ● Preparation of PEG-PNIPAAmc copolymer which act as a suitable temperature sensitive in-situ forming hydrogel (102).
12	Slow and varying response of light-responsive hydrogels to stimulus (light) (55)	● Fabrication of cross-linked polymers of 2-hydroxyethyl methacrylate which were functionalized with azobenzene groups (103). ● Forming an interpenetrating polymer network between polyacrylamide and poly acrylic acid (104)
13	Clogging of needle during injection of pH sensitive and temperature sensitive hydrogels	● Preparation of dual responsive hydrogels (pH/thermo-sensitive hydrogels) (55).
14	pH related activity and solubility and slow sol-gel transition phase	● Chemical modification to improve solubility profile and better mucoadhesiveness (38).
15	Rapid drug release and low drug loading	● Incorporation of hydrophobic monomers such as 4- vinylpyridine or ionic monomers such as N-(3-aminopropyl) methacrylamide to pHEMAd hydrogels in order to increase drug loading capacity and control drug release rate (40).

Continued Table 2.

	Limitations	Solutions
16	The risk of infection and the challenge of surgical implantation of Pre-formed hydrogels or scaffolds using in tissue engineering	● Substitution of injectable hydrogel systems in order to overcome these scaffold limitations (43). Preparation of micro-engineered hydrogels (44).
17	The lack of specific cell adhesive properties of PEG hydrogels as scaffold for tissue engineering	● Cell adhesive modification of PEG hydrogels using extracellular matrix proteins (85).
18	Low DNA or RNA loading capacity in hydrogel network and limited capability of transgene expression for gene delivery purposes	● Incorporation of DNA/polymer polyplexes within PEG hydrogel scaffolds (105). ● Using hyaluronic acid and fibrin hydrogels as scaffolds for DNA/polymer polyplexes (45).
19	The lack of efficiency and suitability as carrier for small molecular weight and hydrophobic active pharmaceuticals	● Synthesis of hydrogel carriers which are fabricated from copolymers of methyl methacrylate and acrylic acid as novel oral drug delivery systems for small molecular weight and hydrophobic active pharmaceuticals (106).
20	Low mechanical strength of calcium alginate hydrogels	● Composition of agar/alginate beads which have the advantage of better mechanical strength and controlled drug release (107).

a Polyethylene glycol – poly(lactic-co-glycolic acid) – polyethylene glycol

b Poly-epsilon- caprolactone (PCL)

c Polyethylene glycol – Poly(N-isopropylacrylamide)

d Poly 2-Hydroxyethylmethacrylate

moieties are available for drug delivery but based on the final purpose of delivery system and route of administration we need to well characterize hydrogel forming polymer. Development of successful hydrogel based delivery system is possible upon knowledge about physiochemical properties of the hydrogel forming polymers and understanding the influencing factors which control the swelling behaviors, hydrophilicity, biodegradability, biocompatibility and targetability of the selected polymer. Hydrogels as drug delivery systems have many advantages including biocompatibility, low toxicity and good swelling behavior but depending on chemical moieties of the gel forming polymers and route of administration some limitations would appear in delivery of active pharmaceuticals such as slow responsiveness of stimuli-sensitive hydrogels, possibility of rapid burst drug release, possibility of drug reactivation, limited hydrophobic drug delivery, low mechanical strength, etc. which should be overcome through different approaches that are suggested by different researchers.

Ethical approval

This review article does not include any animal or human studies done by any of the authors.

Conflict of Interest

None declared.

9. References

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