Drug Design, Development and Therapy

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REVIEW

Hydrogels For Peptide Hormones Delivery: Therapeutic And Tissue Engineering Applications

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy

Mohsen Doostmohammadi[1]
Atefeh Ameri[1]
Reza Mohammadinejad[1]
Negar Dehghannoudeh[2]
Ibrahim M Banat[3]
Mandana Ohadi[1]
Gholamreza Dehghannoudeh[1,4]

[1]Pharmaceutics Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran; [2]Faculty of Arts and Science, University of Toronto, Toronto M5S3G3, Ontario, Canada; [3]School of Biomedical Sciences, Faculty of Life & Health Sciences, University of Ulster, Coleraine BT52 1SA, Northern Ireland, UK; [4]Department of Pharmaceutics, Faculty of Pharmacy, Kerman University of Medical Sciences, Kerman, Iran

Abstract: Peptides are the most abundant biological compounds in the cells that act as enzymes, hormones, structural element, and antibodies. Mostly, peptides have problems to move across the cells because of their size and poor cellular penetration. Therefore, a carrier that could transfer peptides into cells is ideal and would be effective for disease treatment. Until now, plenty of polymers, e.g., polysaccharides, polypeptides, and lipids were used in drug delivery. Hydrogels made from polysaccharides showed significant development in targeted delivery of peptide hormones because of their natural characteristics such as networks, pore sizes, sustainability, and response to external stimuli. The main aim of the present review was therefore, to gather the important usages of the hydrogels as a carrier in peptide hormone delivery and their application in tissue engineering and regenerative medicine.

Keywords: hydrogels, peptides hormones, tissue engineering, drug delivery

Introduction

Peptides and proteins represent an opportunity for therapeutic intervention that closely mimics natural pathways for many physiological functions. Until now, over 60 drugs with peptide structure have been approved in the United States.[1] For example, insulin as a macromolecule has played a notable role in medical practice since 1920s.[1] Formulation, route of the administration, rate and pharmacokinetic profile of peptide drugs in the body showed the vital role in the success of protein drug delivery.[2,3] The oral administration of drugs was the most preferred but unsuccessful. So developing an alternative delivery system for peptides are needed.[4] Studies showed that peptide analogs that were loaded on the desirable systems had the better absorption profile.[5] For example, in hormone therapy, continuous dosing of hormones induces down-regulation of hormone receptors on the target cells that escape the usefulness of the drugs. Thus, discontinuous delivery is rather than continuous.[6] The smart delivery systems that release drugs by triggering through external stimuli are of great use in the case of peptide hormones (PHs) such as insulin, calcitonin, and human growth hormones (hGH).[7,8] Hydrogels are cross-linkable water-swollen polymeric network, produced by the simple reaction of one or more monomers.[9] Hydrogels protect and deliver peptides due to their unique physical properties include continuous release that resulted in the maintaining a high local concentration of peptides over a long period of time.[10,11] Nowadays, natural hydrogels are gradually replaced by synthetic hydrogels, which have a long half-life, high capacity water absorption, and high gel strength.[12]

Correspondence: Mandana Ohadi; Gholamreza Dehghannoudeh
Pharmaceutics Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran
Tel +98 34 31325243; +98 34 31325014
Fax +98 34 31325003
Email mandanaohady@gmail.com; ghr_dehghan@kmu.ac.ir

submit your manuscript | www.dovepress.com
DovePress
http://doi.org/10.2147/DDDT.S217211

Gels are formed by chemical or physical process.[13] Chemical gels are formed by cross-linked polymeric network while physical gels formed by non-covalent interactions between the chains.[14] Physical gels known as stimuli-sensitive or smart gels are divided into thermo-sensitive, pH-sensitive or analytic-sensitive hydrogels.[15] Thermo-sensitive hydrogels are very interested in biomedical applications, because of temperature can be controlled easily.[16,17] So, the main goal of this review was to summarize some important hydrogels used for delivery of hGH, calcitonin, and insulin as some examples for sustain release of PHs.

Hormones

Hormones are produced by endocrine glands and secreted into the blood circulation and could act at some distance organs.[18] According to the chemical structures, hormones are categorized into two main groups of steroids, e.g., cortisol, aldosterone, and progesterone; and peptides, e.g., insulin, growth hormone, and calcitonin.[19,20]

Peptide Hormones (PHs)

The PHs are a group of small molecules with the polypeptide chain. The hypothalamus, besides its thermo-regulation activity, is responsible for the production of some PHs. PHs are transported and stored in the pituitary gland and have regulatory effects on the synthesis of other hormones produced by the anterior pituitary.[21] This function was caused to calling them as releasing factors or inhibitory factors.[22–24] Some PHs like insulin are stored within vesicles inside the cells and secreted into the blood after receiving specific simulations like high blood glucose.[25] Regarding PHs are hydrophilic, they cannot across through phospholipid membrane, so the specific receptors on the target cells are needed.[5] Nowadays, PHs with the special ligand are produced by applying the genetic engineering technologies. However, these targeted PHs showed significant healing effects on patients, but there are still some limitations such as degradation in the gastrointestinal (GI) tract, short half-life, and poor adsorption.[19,22]

Stability Features Of PHs

The secondary, tertiary and quaternary structures of peptides are maintained by weak non-covalent interactions, so any changes in these interactions could lead to destabilization or denaturation of peptides.[26] For example, the changes of pH, temperature, ionic strength, and pressure parameters could induce the aggregation, precipitation, and inactivation of the PHs.[26–28] Therefore, to improve the chemical and physical stability of the PHs several strategies are developed. For instance, the site-specific mutagenesis to reduce peptides enzymatic degradation or glycosylation to enhance oral absorption, stability, and activity of the therapeutic peptides are being used (chemical strategy; PEGylation).[28,29] Adding absorption enhancers such as surfactants, chelating agents, and fatty acids are commonly used (physical strategy; nanoparticles, liposomes, pH-responsive composites).[26,30] Further strategies to improve the activity of the PHs are listed in Table 1.

New Drug Delivery Systems For Peptides

Polymer conjugation is used to reduce the proteins immunogenicity and their physiological environment stability through covalent interactions and retention in circulation, respectively.[45] For instance, pluronic hydrogels were used as carriers in several routes of administration.[46] Also, pluronic micelles could concentrate the proteins at the particle surface and the stability and bioactivity of the proteins are higher than the aqueous phase.[47] Polystyrene beads are also proposed to be safest particles for protein adsorption.[48] Liposomes are reported as good proteins carriers because of their size, aqueous core, biocompatibility and biologically inertness, weak immunogenic nature, and limited toxicity that protect peptides in the GI.[49,50] For instance, Archaeosomes™ is reported as a new formulation of liposome that shows high stability.[51] Combination of the silica and liposomes could protect proteins (insulin) from enzymatic degradation (lipolytic) and prolong protein release in simulated GI conditions.[52] Respiratory tract is a non-invasive route to adsorb the macromolecular drugs due to reduce acidity and proteolytic activities and a thinner mucus layer. Inhalation of the peptides with relatively low molecular mass such as insulin is well, while systemic administration of these macromolecules through the respiratory tract is often a challenging problem due to biological barriers.[53] Nanoparticles show the potential to overcome the biological barriers because of their small size, avoiding clearance and phagocytosis.[54] For instance, insulin was encapsulated by using the layer-by-layer technique, administrated through the respiratory tract, resulted in a good-sustained level of drug in the blood.[55] Also, the inhaled insulin in the

Table 1 Using Strategies To Improve The Activity Of The PHs

Type of PHs	Therapeutic Class	Instability Agents	Solution	Delivery Route	Ref.
Growth hormone	Growth hormone	Physiological barriers: enzymes, mucus, and pH of the GI tract	**Nanoparticles** To improve the biologicals absorption by the permeation enhancers and defeating metabolism of peptides in the GI tract	Oral	26
			Liposomes Liposomes formulated with cetylpyridinium-chloride (CpCl) improved hGH oral bioavailability	Oral	31
			PEGylation Thiol modification by PEGylation improvement of their chemical stability and biological properties	Oral	26
		Metal-catalyzed-oxidation (MCO)	Minimizing exposure to oxygen, by reducing the headspace in the vial	Oral	23
		Deamidation-asparagine, glutamine	The pH value of the solution was reported to have an effect on the deamidation of Asn residues in hGH	Oral	28,32
	Growth hormone	Iosmerization-Asparagine-X, Aspartic Acid-X	-Changes in temperature and pH buffer species-Ionic strength	Oral	28,32
		Disulfide-scrambling/ oligomerization cysteine	Changes in temperature and pH buffer species Ionic strength	Oral	28,32
Salmon calcitonin	Antiosteoporotic	Physiological barriers: enzymes, mucus, and pH of the GI tract	**Peptelligence technology** Citric acid and lauroyl-l-acylcarnitine to improve the biologicals absorption by the permeation enhancers	Oral	29,33,34
			Eligen technology 8-(N-2-hydroxy-5-chloro-benzoyl)-amino-caprylic acid (5-CNAC) to improve the biologicals absorption by the permeation enhancers	Oral	34
			Axcess technology Improvement through the permeation enhancers such as Hydrophobic aromatic alcohols, butylated hydroxyalcohol (BHA), butylated hydroxytoluene (BHT) and propyl-gallate solubilized	Oral	34
	Antiosteoporotic	Physiological barriers: enzymes, mucus and pH of the GI tract	Citric acid, phenylethyl alcohol, benzyl alcohol, PEG sorbitan monooleate, to improve the biologicals absorption by the permeation enhancers		34
			PEGylation The enhanced resistance against pancreatic peptidases and brush-border peptidases and improvement of their chemical stability and biological properties	Nasal	26
			Oracal™ have the permeation enhancer and the coated vesicle in its structure		26

(*Continued*)

Table 1 (Continued).

Type of PHs	Therapeutic Class	Instability Agents	Solution	Delivery Route	Ref.
			N-acetylation Improved oral bioavailability, marginally improved resistance to trypsin and leucine aminopeptidase, enhanced membrane permeability	Oral	30
	Regulating calcium ion concentration	β-Elimination	Changes in temperature and pH Buffer species oxidizing agent	Oral	32
		High elimination rates of the drug in contact with its absorption sites	**Calcitonin-containing chitosan-aprotinin multilamellar vesicles (MVL)** Chitosan–aprotinin coated liposomes	Oral	31
		Deamidation	The pH value of the solution was reported to have an effect on deamidation. pH 3–5, increased solvent viscosity	Oral	32
		Oxidation	Deamidation reaction is dependent on varying pH values. The pH value (pH < 7) was significant in the reaction medium. Other factors, including air exclusion, antioxidants, chelating agents, and polyols affected oxidation	Oral	32
		Aggregation/fibrillation	Lower concentration, minimal mechanical stress, organic solvents, alkyl saccharide, alkyl polyglycoside	Oral	32
Insulin	Antidiabetic, hypoglycemic hormone	Physiological barriers: enzymes, mucus, and pH of the GI tract	**POD (patented protein oral) delivery technology system** To improve the biologicals absorption by the permeation enhancers	Oral	34
			Axcess™ delivery technology system To improve the biologicals absorption by the permeation enhancers	Oral	34
			RapidMist technology Mixed micelles made up of a combination of enhancers. To improve the biologicals absorption by the permeation enhancers	Oral	34
			CPE-215 (Cyclopenta decalactone) technology To improve the biologicals absorption by the permeation enhancers	Oral	34
			pH-responsive nanoparticles Helping to release the protein in the small intestine and reduce the degradation by enzymes as well as enhance of absorption.	Buccal	26,30
	Antidiabetic, hypoglycemic hormone	Physiological barriers: enzymes, mucus and pH of the GI tract	**pH dependent and mucoadhesive nanoparticles (Dextran sulfate/chitosan nanoparticles)** To enhance intestinal residence time and release target protein in intestine	Nasal	26,35

(*Continued*)

Table 1 (Continued).

Type of PHs	Therapeutic Class	Instability Agents	Solution	Delivery Route	Ref.
			Micro particles Mucin and sodium alginate have used to prepare Insulin-loaded micro particles	Peroral/ Oral	31,36
			Liposome An alkyl/alkenyl sulfate comprised of protein/peptide	Peroral/ Oral	36,37
			Insulin-containing multivesicular liposomes (MVLs), adding of novel chitosan and carbopol to MVLs as sustained release protein delivery systems	Oral	31
	Antidiabetic, hypoglycemic hormone		**Microsphere** A protein microencapsulated with a water-based enteric coating	Oral	38
			Microparticles Enteric-coated capsules/tablets for oral delivery of protein, polypeptide or a peptide drug	Nasal; ocular	39
	Antidiabetic, hypoglycemic hormone	Physiological barriers: enzymes, mucus and pH of the GI tract	**Microemulsion** Fatty acid formulations for oral delivery of proteins and peptides	Oral	39
			Oral capsule using non-acylated amino acids as carriers (Eligen™)	Oral	29,39
			Macrosol™ W/O (Water/Oil) microemulsion technology (Macrulin™)	Oral	29
			Oral formulation of recombinant human insulin (AI-401)	Oral	29,39
			Mixed micellar solution (Oral-lyn™)		26,29
		Deamidation	Deamidation reaction in peptides or proteins is pH-dependent	Oral	32,40
		Isoelectric precipitation	Stresses such as temperature and moisture resulted in conformational changes, linear aggregation, and formation of a viscous gel	Oral	32
	Antidiabetic, hypoglycemic hormone	Physiological barriers: enzymes, mucus and pH of the GI tract	To reduce degradation by enzymes and enhance absorption in the small intestine	Buccal	39
			Nanoparticles Ligand-specific binding and uptake. The effectiveness of insulin conjugated vitamin B12-coated nanoparticles in diabetic rats. (Oradel™)	Oral	26,30
		Physiological barriers: enzymes, mucus and pH of the GI tract	**PEGylation** PEGylated products of insulin exhibited low degradation rate by elastase and pepsin in contrast to unmodified products of insulin	Oral	26,30

(*Continued*)

Table 1 (Continued).

Type of PHs	Therapeutic Class	Instability Agents	Solution	Delivery Route	Ref.
	Antidiabetic, hypoglycemic hormone	Physiological barriers: enzymes, mucus and pH of the GI tract	Insulin analog NN1954, GIPET (GI permeation enhancement technology): To improve the biologicals absorption by the permeation enhancers	Intestine	24
			Hexyl-insulin monoconjugate 2 (HIM2), hydrophobization, to increase lipophilicity of peptides Conjugation of the insulin molecule to the 1,3-dipalmitoylglycerol containing a free amino acid groups of glycine, phenylalanine and lysine molecule. Improvement of their stability against the enzymatic degradations.	Oral	41,42
			Oral HDV-insulin (HDV-I), Nanocarriers liposomal delivery system		26
Glucagon-like peptide-1 (GLP-1)	Anti-diabetic medication (type 2 diabetes mellitus)	Physiological barriers: enzymes, mucus and pH of the GI tract	**GIPET® technology (Gastrointestinal Permeation Enhancement Technology)** To improve the biologicals absorption by the permeation enhancers.	Oral	37
			Emisphere™ (n-(8-[2-hydroxylbenzoyl]amino)caprylic acid) (SNAC) carrier molecule improved membrane penetrability	Oral	30
			Glp-1/iDPP4 delivery multifunctional composite system At first, GLP-1 loaded in PLGA nanoparticles and encapsulated within the HPMC-as pH-sensitive polymer, and followed by loaded with the dipeptidyl peptidase-4 inhibitor (iDPP4)		43
			Novel hybrid hyaluronan (HA) hydrogel encapsulating nanogels Protein nanocarrier used for sustained delivery of glucagon-like peptide-1	Oral	44
			Cell penetrating peptides L- and D-penetratin		43
	Anti-diabetic medication (type 2 diabetes mellitus)	Physiological barriers: enzymes, mucus and pH of the GI tract	**PEGylation** PEGylated products of Glp-1 exhibited enhancing absorption and enzyme resistance	Oral	43
			Biotinylation To modify the peptide surface using biotin (vitamin H). To resist in intestinal enzymes To increase the intestinal absorption		43

form of lyophilized powders based on the amphiphilic polymers was developed.[56]

Cell-penetrating peptides (CPPs) also known as short peptide sequences with positive charge that synthesized easily and have the potential for sequences modification. The high internalization and low cytotoxicity are the bold characteristics of cell-penetrating peptides.[57] To improve peptides and proteins delivery to the central nervous system, combination of the systemic administration of the drug and transient osmotic opening of the blood–brain barrier (BBB) was applied as a strategy.[58]

Hydrogels For Peptide Hormone Delivery

Different types of materials have been developed for the hormone formulation industries.[59] PHs have great role in the development of the human brain by regulating specific genes expression. PHs have low stability during formulation and storage, which make their formulation challenging.[60] Controlled delivery of peptide drugs, especially agents with high molecular weight has great importance.[11] Recently concerted efforts have been made for the development of a stable formulation for non-invasive delivery of hormones through oral, skin or nasal methods.[34]

Hydrogels are a network of cross-linked, water-soluble polymer chains that are insoluble in water and biological fluids but have water as their dispersion medium.[61] The most advantages of hydrogels are biocompatibility potential, low toxicity, large-scale bioactivity and multi-functionality, controlled drug release, hydrophobicity, smart drug delivery, and biodegradability.[62] Hydrogels structurally are too similar to natural tissue because of their significant water content. Drugs could be loaded on the hydrogels as well because of their porous nature. For instance, interpenetrating polymer networks (IPN) hydrogels were applied as drug delivery controller due to their mechanical strength and swelling/de-swelling response.[27] Also, hydrogels could be used as injectable due to their biocompatible and biodegradable features. Hydrogels are able to tolerate changes in the pH and temperature which could protect drugs against harsh environmental conditions. For example, Phan et al[63] used the biodegradable, temperature, and pH-sensitive injectable hydrogels that resulted in the sustained delivery of hGH and well-ordered degradation of the gel matrix without any swelling at the injection site and its surrounding tissue.[63] In another study, Schoener et al[64] applied a hydrophilic pH-responsive hydrogel hybrid with hydrophobic nanoparticles due to cytocompatibility.

Disadvantages of the hydrogels include non-adherent to cells and tissues; they may need to be protected by a secondary covering. They are expensive for tissue engineering and regenerative medicine. Sterilization of hydrogels is difficult and time-consuming. Loading of drugs and cells into hydrogels are difficult.[65]

Hydrogels As Carrier For Human Growth Hormone

Growth hormone is applied to treat children with growth hormone deficiency (GHD) that caused due to isolated hormonal deficiency, central nervous tumor, pituitary hormone deficiency, and cranial irradiation. Also, growth hormone is used for Prader–Willi and Turner syndromes, AIDS-associated weight loss, and renal insufficiency.[66,67] The accepted administration way of hGH is injection.[68] Even hGH replacement therapy is accepted by scientists as a good treating protocol, but still, injection is the best way.[69] Till now, more studies were done to find the developed delivery systems that have a low initial burst and high bioavailability and therapeutic effects.[70,71] Hydrogels seem to act as an excellent delivery systems for hGH because of their biodegradable, thermo-sensitive, and pH-dependent gelation.[63] PACU poly(amino carbonate urethane)-based pH-/temperature-sensitive injectable hydrogel was synthesized for sustain delivery of hGH.[63] The poly(methacrylic acid-g-ethylene glycol) [P(MAA-g-EG)] is one of the most extensively used hydrogels for oral peptide delivery.[72–74] Mucoadhesive and retention were enhanced in the small intestine by PEGylation of the methacrylic acid (MMA) hydrogels. Copolymerization of MMA with hydrophilic monomers such as PEG and N-vinyl pyrrolidone could trigger the pH.[71] Poly (methacrylic acid-co-N-vinyl pyrrolidone) hydrogel could act as an efficient delivery system for hGH orally, which showed the good release of the drug during the first hours of the administration in the upper small intestine.[75] In another study, poly(methacrylic acid-co-N-vinyl pyrrolidone) microparticles showed no release of hGH under gastric conditions, so it can conclude that the synthesized composite is suitable for high molecular weight drugs.[75]

Hydrogels of poly(vinyl alcohol) (PVA) and poly (acrylic acid) (PAA) in combination with collagen (C) and hyaluronic acid were used in hGH delivery.[76] The release profile was in the linear phase during the first

3 days and then followed rapidly. A delivery system composed of negatively charged; poly-b-amino ester urethane (PAEU) copolymer hydrogel and positively charged; 2D-layered hydroxide nanoparticle (LDH), was developed to overcome the limitation of hGH such as premature degradation and low half-life. Releasing profile of hGH loaded on the mention hydrogel showed the sustained rate of drug release in in vitro and in vivo; 13 and 5 days, respectively.[77]

Sucrose acetate iso-butyrate was combined with polylactic acid (SABER) as a new composite was investigated to deliver hGH that acted as weight-based dosing.[78] hGH burst release was significantly reduced by enhancing the content of polylactic acid that is because of the diffusional barriers around the proteins after floating in the aqueous environment.[78] Also, combination of the hydrogels such as poly(lactic acid-*co*-glycolic acid) (PLGA) reduced the immunogenicity response.[63] The surface erosion characteristics of the hydrogels could be controlled by incorporation of PEG into them.[63] For instance, PEGylation of fluorocarbon end groups attachment (R_f-PEG) hydrogel was done to deliver hGH.[79] In the presence of N-methyl pyrrolidone, R_f-PEG made gel quickly, because organic solvent that diffuses into the environment. Studies showed that hGH maintained in the active form inside the hydrogels and was released during 2 weeks without any aggregation. Furthermore, the ability of this hydrogel in the delivery of two other proteins including bovine serum albumin (BSA) and g-globulin was reported.[80]

Hydrogels As Carrier For Calcitonin

Injection and oral use are the conventional administration of the calcitonin.[81,82] Since the oral administration is too much favorable and improves the life quality, using hydrogels to formulate calcitonin hormone act as an interesting way to protect hormone from the harsh condition of the gut and intestine. Moreover, hydrogels could act as a control release composite.[81,83] Since the upper small intestine and dominant stimulus are the most interesting parts to absorption of the oral administration peptide, because of the acidic environment. So, the attention to use of the pH-sensitive hydrogels is increasing. For example, salmon calcitonin was loaded on (P(MAA-g-EG)) hydrogel as a pH-sensitive compound that acted as constant release.[84] The polymerization in this hydrogel is performed by the interaction of oxygen from graft chain and acidic groups. This lead to hydrogel condensation and the collapse of the network in an acidic environment, while gradually with enhancing the pH, the inter-polymeric bonds dissociate after ionization of groups and the water is allowed to enter to the network.[85] In another study, the high loading efficiency of complexation hydrogels (P (MAA-g-EG)) which was previously used for insulin oral delivery was demonstrated.[86] The polymer loaded with calcitonin showed pH-sensitive and complexation/decomplexation release behavior. The entrapped calcitonin retained in the polymeric matrix at pH 1.2, but it released immediately at high pH (pH 6.8). Furthermore, it was shown that P(MAA-g-EG) hydrogels showed the high affinity to peptide drugs with bulky structure.[78] P(MAA-g-EG) also presented some adhesive properties to the mucosal membrane with no adverse effect on this tissue.[86]

Hydrogels As Carrier For Insulin

Insulin had been used in several ways such as pulmonary, nasal, buccal and oral, rectal, ocular and transdermal, vaginal, intrauterine, and injection.[87,88] Oral administration of insulin has been estimated to be more convenient in enhancing patient adherence and its absorption imitates insulin secretion under physiological conditions and is effective on the hepatic glucose production and reduce the danger of hypoglycemia-related to the peripheral insulin injection.[89] But new oral insulin administration devices include liposomes, microcapsules, beads, hydrogels, and chemical modifications of the molecule showed the numerous challenges that have failed to improve their outcomes.[90,91] Therefore, co-polymeric hydrogel microparticle of P (MAA-g-EG) and pH-sensitive nanoparticles have been demonstrated.[33,92–95] For instance, the oral form of the pH-sensitive nanoparticles composed of poly(g-glutamic acid) and chitosan showed high bioavailability in diabetic animal models.[96]

Also, super porous hydrogel (SPH) and SPH composite (SPHC) polymers enhanced the gut absorption of insulin in healthy pigs.[97] Further, a pH-temperature-sensitive hydrogel composed of poly(β-amino ester)–poly(ε-caprolactone)–poly(ethylene glycol)–poly(ε-caprolactone)–poly(β-amino ester) (PAE-PCL-PEG-PCL-PAE) pentablock copolymer, as a sustained injectable system was assessed.[98]

The pH/thermosensitive polymeric beads based polymers of N-isopropylacrylamide (NIPAm), butyl methacrylate (BMA), and acrylic acid (AA) were applied to release insulin.[99] Results showed that the molecular weight of the polymers effects on the rate of release.[100] The insulin was entrapped in polymeric matrix by cross-linking through condensation of hydroxyl groups of Kappa carrageenan (KC) and vinyltriethoxysilane

(VTESi). Furthermore, studies on the structure of hydrogel revealed that by enhancing the crosslinker (KC) concentration, marked decrease in swelling ration of hydrogel was obtained which finally led to slow peptide release rate of hydrogel.[99] James and coworkers have prepared a smart polymeric "intelligent" delivery systems capable of sustained release of therapeutic macromolecules.[101] The nanocarriers, polymeric nanoparticles, have shown benefits for peptide drug delivery following oral, nasal, pulmonary, parenteral, transdermal, and ocular doings.[102] PCL–PEG–PCL, chitosan (CS), and poly(l-lactide) NPs achieved higher insulin loading and were employed to improve bioavailability and hypoglycemic activity of insulin *via* oral route.[103,104] The chitosan-N-acetyl-L-cysteine (CS-NAC) NPs and hybrid poly-oligosaccharide NPs comprising CS and cyclodextrins were applied as nanocarriers for nasal insulin delivery.[105,106] Nanocarriers such as CS NPs have been suggested as an excellent formulation for local and systemic delivery of insulin following pulmonary route.[102,107] The polymeric nanocarriers have been used to enhance solubility, bioavailability, and prolonged circulation times of insulin.[108] The rectal form of insulin composed of acrylic hydrogels containing absorption enhancers was applied in in vitro and in vivo environment.[109]

Hydrogels As Carrier For Glucagon-Like Peptide-1 Receptor Agonist's

Application of the anti-diabetic drugs has been faced with several problems. For example, injection of insulin should be done before the meal, need repetitive every day and may lead to hypoglycemic symptoms. Therefore, to solve these problem GLP-1 analogs and their corresponding receptors (exendins) can be used.[110] Exendin-4 is the safest exendin drug and belongs to incretin mimetics. It is demonstrated that this compound is able to enhance glucose-dependent insulin secretion and induce satiety.[111,112] Byetta®, a synthetic formulation of Exendin-4 (Exenatide (EXT)) has been approved for type II diabetes. Microsphere formulation (Bydureon®) has been developed with only one injection per week.[113] Furthermore, less side effects were reported for Bydureon® than Byetta®. Until now several kinds of thermos-gels such as PEG and poly-phosphazene have been developed for protein delivery.[114,115] The potency of poly(lactic acid-co-glycolic acid)–poly(ethylene glycol)–poly(lactic acid-co-glycolic acid) triblock co-polymers in delivery of EXT has been investigated by Li et al.[116] In this formulation, zinc acetate was introduced to this formulation to improving drug release of EXT.[116] A new hydrogel system of EX-4 using poly (organophosphazenes) was developed which is hydrophilic, easy and has high capacity of protein loading and easy administration.[117] Poly(organophosphazenes) by conjugating protamine was used to enhance hydrogel interaction with EX-4.[118] In another study, poly(ε-caprolactone-*co*-glycolic acid)–poly(ethylene glycol)–poly (ε-caprolactone-*co*glycolic acid) (PCGA-PEG-PCGA) triblock thermos-sensitive co-polymers were used to sustain delivery of Liraglutide (Lira).[119]

Hydrogel-Based Peptide Hormone Delivery For Tissue Engineering And Regenerative Medicine

Due to their unique structural and physicochemical characteristics of hydrogels, they are considered as pioneer candidate in the tissue engineering.[120,121] Gels are widely used in cell culture because of their 3D network structure and high permeability. For instance, hydrogel scaffolds are used for simultaneous seeding of cells because of their shape, porosity, and surface morphology.[122] Since the hydrogel scaffolds are too similar to the extracellular matrix, an opportunity was created to overcome various challenges in tissue engineering.[7]

Calcitonin has diverse physiological functions such as regulation of calcium homeostasis and bone metabolism. The peptide hormone effectively prevents bone loss. Calcitonin upregulates collagen expression and inhibits metalloproteases.[123] Calcitonin affects extracellular matrix synthesis and has therefore been clinically used in the treatment of postmenopausal osteoporosis.[124] Recently, Liu et al[124] prepared the salmon calcitonin and oxidized calcium alginate (sCT-OCA)-loaded poly(d,l-lactic acid-co-glycolic acid)-b-poly(ethylene glycol)-b-poly(d,l-lactic acid-co-glycolic acid) (PLGA-PEG-PLGA) hydrogel. The thermo-sensitive triblock copolymer hydrogel exhibited sol–gel transition at body temperature and has therefore been used for long-term anti-osteopenia treatment in rats. sCT was released by degradation of the hydrogel. The system reduced serum calcium and bone trabecula reconstruction in the treatment of glucocorticoid-induced osteopenia in rats (Figure 1).

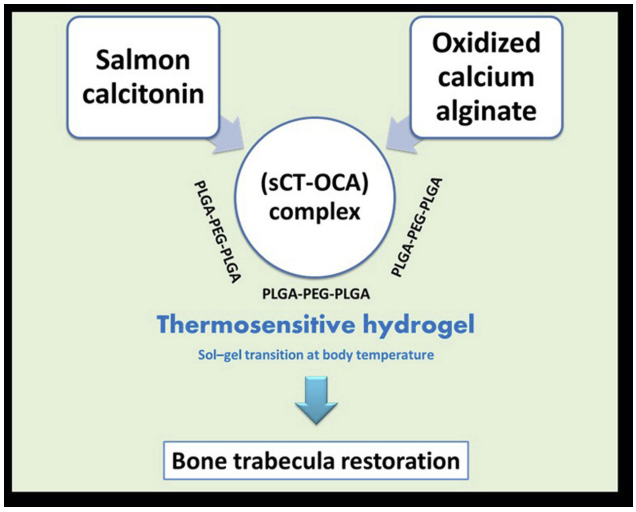

Figure 1 The PLGA-PEGPLGA hydrogel for controlled sCT release.
Note: Data from Liu et al.[124]

The FDA approved regulator of calcium homeostasis, parathyroid hormone (PTH) possesses anabolic effects on bone and therefore plays an important role in bone metabolism and regeneration.[125] Numerous studies have shown that once-daily injections of PTH enhance the bone healing in vivo.[126] In a study, Park et al[10] presented a new strategy for improved clinical application of parathyroidectomized (PTX). They enhanced the sustained release of PTX using in situ-forming gelatin-hydroxyphenyl propionic acid hydrogels (GHH) to control mechanical stiffness. They reported the best-sustained release of PTH in GHH-embedded differentiated tonsil-derived mesenchyme stem cells (dTMSCs). The hydrogels improved blood calcium homeostasis and treated hypoparathyroidism effectively. Interestingly, undifferentiated TMSCs also incorporated into GHH have released PTH in a sustained manner. PTH was used to enhance osteoblasts proliferation.[127] They showed that stromal precursor antigen-1 (STRO-1) human periodontal ligament stem cells (hPDLSCs) expressed higher levels of the PTH-1 receptor (PTH1R) than STRO-1(−) hPDLSCs. In addition, intermittent PTH treatment enhanced the expression of PTH1R and osteogenesis-related genes in STRO-1(+) hPDLSCs. The results showed that the mineralization ability and alkaline phosphatase activity increased in PTH-treated cells. Intermittent PTH treatment improved the capacity for STRO-1(+) hPDLSCs to repair damaged tissue and ameliorate the symptoms of periodontitis. The effects of parathyroid hormone-related protein (PTHrP) (1–37) were investigated and the degradable implant was suggested as an attractive strategy for improved bone regeneration in aged and diabetic rats.[128]

Conclusion

The usages of the pharmaceutical proteins (large molecule) as a therapeutic agent have been increased strangely because of their advantages. Because of the high proteolithic activity and low pH of the stomachs, proteins are destabilized and degraded oral, which resulted in the loss of biological activities. So, oral administration of proteins is a challenging route. Hydrogels seem to be suited to enhance efficacy, reduce dosing interval, and provide a more convenient dosage route for large and labile proteins. So, protein-loaded hydrogels are explored to increase the therapeutic outcome. Critically, biocompatibility depends on the interactions between tissue and material interface. Therefore, hydrogels have potential in overcoming the unique formulation challenges of biotherapeutics.

Acknowledgment

The authors would like to thank Kerman University of Medical Sciences (KMU) for facilitating relevant research into the conclusions related to this study.

Disclosure

The authors report no conflicts of interest in this work.

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