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Research Article

The synthesizing of different hydrogel nanocarriers for oral ınsulin delivery

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ABSTRACT

Diabetes is seen as the global health problem of the world due to the high risk of complications and the increasing prevalence of death. The routine diagnosis of diabetes is the injection of insulin. This treatment has a lot of side effects known to the patient (infection at injection sites, irritation, etc.). In order to overcome such conditions in the treatment of diabetes and provide faster recovery, many different delivery systems for insulin are being studied. Hydrogels are interesting polymers with hydrophobic structure that can be designed in 3D networks for oral insulin delivery. In this study, we studied the synthesis of biodegradable, biocompatible, low-toxicity therapeutic hydrogels. Acrylamide (ACR):carboxymethyl cellulose (CMC) (ACR/CMC), Acrylamide (ACR): Chitosan (Chi) and Chitosan:glutaraldehyde hydrogels were prepared. The CMC was used in acrylamide-based hydrogels for both comonomer and biocompatibility. The swelling capacity of hydrogels and the in vitro release of insulin from hydrogels were studied at different pH. Insulin release studies have shown that ACR/CMC hydrogels are a good and new alternative as an oral insulin carrier.

Keywords: Hydrogel, insulin, delivery systems, diabetes, acrylamide.

Oral insulin taşınımı için farklı hidrojel nanotaşıyıcıların sentezlenmesi

ÖZ

Diyabet, yüksek komplikasyon riski ve buna bağlı olarak artan ölüm prevalansından dolayı dünyanın global sağlık problemi olarak görülmektedir. Diyabetin rutin tedavisi insulin enjeksiyonudur. Bu tedavinin hasta da bilinen oldukça fazla yan etkisi mevcuttur (enjeksiyon bölgesinde enfeksiyon, iritasyon, vb.). Diyabetin tedavisindeki bu tip durumları bertaraf etmek ve daha hızlı iyileşme sağlamak için, insülinin birçok farklı taşınım sistemleri çalışılmaktadır. Hidrojeller, oral insülin taşınımı için 3D ağlarda tasarlanabilen hidrofobik yapılı ilgi çeken polimerlerdir. Bu çalışmada biz, biyo parçalanır, biyo uyumlu, düşük toksiteli teropötik hidrojellerin sentezini çalıştık. Akrilamid (ACR): karboksimetil selüloz (CMC) (ACR/CMC), Akrilamid (ACR): Kitosan (Chi) ve Kitosan:glutaraldehid hidrojelleri hazırlandı. CMC hem komonomer hem de biyouyumluluk için akrilamid tabanlı hidrojellerde kullanıldı. Hidrojellerin şişme kapasitesi ve hidrojellerden İnsulinin in vitro salınımı farklı pH'larda çalışıldı. İnsulin salınım çalışmaları, ACR/ CMC hidrojellerinin oral insülin taşıyıcı olarak iyi ve yeni bir alternatif olduğunu göstermiştir.

Anahtar Kelimeler: Hidrojel, insulin, taşınım sistemleri, diyabet, akrilamid.

1. INTRODUCTION

Diabetes is the most important health problem all over the world. The classification of diabetes is complex but there are three main types of diabetes; type I diabetes (T1DM), type II diabetes (T2DM) and gestational diabetes. The most diabetes patients have commonly Type II diabetes, and they include nearly 90% of diabetic persons. T2DM is a complex disease associated with pancreatic β- cell dysfunction and varying degrees of insulin resistance. Moreover, the control of insulin level and traditional treatments are unsatisfactory. Because macro (stroke, cardiovascular disease, coronary artery disease, cerebrovascular disease, diabetic foot)

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and micro (retionapathy, cataract, nephropathy, neuropathy) vascular complications of T2DM patients can vary from person to person and may reduce the qualities of the lifes of the patients and their families. The common anti-diabetic drugs are metformin, sulfonylureas, glinides, α-glucosidase inhibitors, GLP-1 agonists, thiazolidinediones, DDP-4 inhibitors and insulin. To control blood glucose level, exogenous insulin must be taken by who are suffering insulin deficiency. Insulin is a polypeptide hormone that consists of 51 amino acids in two chains (A chain, 21 amino acids; B chain, 30 amino acid), joined together by two disulfide bonds that helps in regulating the uptake and storage of glucose in the liver and muscles. It is produced by ß-cells of pancreas and released into the blood via exocytosis process. There are three major sources of insulin preparations based on different diagnosis strategies; rapid-acting insulin (to manage meal time blood glucose), long-acting (to manage daily basal insulin needs) and pre-mixed insulin. A standard treatment of T2DM patients who are suffering with insulin deficiency is repeated subcutaneous injections of insulin. Multiple insulin injections cause bad shortcomings; local skin irritation, fat deposits at injection points, stress, so on. All of these disadvantages lead that the researchers research new alternative routes for delivery of insulin and other peptide drugs. Oral, pulmonary and nasal delivery of insulin are other alternative routes. The most promising challenge is oral delivery of insülin.[1-3] The problems of oral delivery insulin systems are the physical instability of insulin at different conditions (acidic pH, elevated temperature, solvent, buffer media), the enzymatic degradation at gastrointestinal track (the protein structure of insulin) and rapid systemic clearance (concentration). Many techniques have been developed to overcome these problems. To overcome the mentioned problems above, some modifications can be done. Just like that, to overcome digestive destruction, the surface of nano carriers are biotinylated or PEGylated. For the solution of transformation and enhancing adsorption, cell-penetrating peptides, muco- adhensive polymeric systems, oral micro particle delivery systems are used. And the last way is to use the natural and synthetic polymers (liposomes, inorganic particles, nano-emulsions and hydrogels).[4] Natural polymers are studied more than others because they exhibit higher biocompatibility, biodegradability, safety, low toxicity and better physiological stability.[5-7] The known disadvantages of nanocarrier systems are their particle size, coating, modification, inherent characteristics of nanoparticles, and the biological degradation. One of the most attractive polymers for oral delivery systems is hydrogels. Hydrogels are considered as super absorbent because they are able to absorb large quantities of water or the mixed environmental solvents. 2D and 3D compositions of hydrogels change with the composition of polymerization mixture (cross linker, monomers, comonomers, solvent). An injectable hydrogel can undergo sol-gel transformation in the body and be utilized for the controlled release of therapeutics, thus reducing the dosing frequency and side effects.[8-16]

The aim of our study is to synthesis promising and improvable different insulin oral delivery nanocarriers. To obtain biocompatible, low toxicity and biodegradable acrylic based hydrogels, it was studied with carboxyl methylcellulose (CMC) and chitosan. To contribute the results, the conventional chitosan insulin nanocarrier is also studied. PH stability, swelling properties (water, buffers) and in vitro insulin release in glucose medium were performed to analyze the ability of nanocarriers to be used as oral insulin delivery. *In vivo* analysis is planned for further experiments.

2. MATERIALS AND METHODS

2.1. Materials

The acrylamide (ACR), N, N- Methylenebisacrylamide (N,N-MBA), chitosan (Chi) (low molecular weight; 75-85% deacetylated) , carboxylmethyl cellulose (CMC) (0.60-0.95 substitution**),** glutaraldehyde, Tetramethylethylenediamine (TEMED), ammonium persulfate (APS) were purchased from Sigma (USA). All the other chemicals were analytical grade.

2.2. Hydrogel synthesis

Different hydrogel compositions and different ratio of ACR/CMC, ACR/Chi and Chi/glutaraldehyde were studied.

2.2.1. Acrylamide based hydrogels

For biodegradability and biocompatibility, CMC was used as comonomer.[17-20] The different ratios of ACR/CMC [1:0.01; 0.1:0.01; 1:0.02] were dissolved in distillated water and mixed with appreciate weight of N, N-MBA (crosslinker) (10 mg). To start radical polymerization, TEMED/APS was added. After 30 min at 37°C, the hydrogel samples were ready to use. All samples were washed in excess water to remove unreacted components. In this study, all of the samples were gelated 100% and no extractable monomers were observed. To change hydrophilic character and the strength of acrylamide-based hydrogels, chitosan is used as comonomer. The toxicity of hydrogels is minimized by using chitosan. The different ratios of ACR/Chi [1.5:0.02; 1:0.02; 0.1:0.02] were dissolved in distillated water and mixed with appreciate weight of N,N-MBA (10 mg) (crosslinker). To start radical polymerization, TEMED/APS was added. After 15 min at 37°C, the hydrogel samples were ready to use. Some gellating problems were occurred since hydrogel synthesis from. While preparing ACR/Chi hydrogels, different amount

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ACR/Chi. The hydrogels did not gellated completely of N,N-MBA was studied but the best result was obtained for only ACR/Chi (1.5:0.02) and 10 mg N,N-MBA. All samples were washed in excess water to remove unreacted components.

2.2.2.Chitosan based hydrogels

The chitosan hydrogels were crosslinked with glutaraldehyde. The constant amount of chitosan (3%, 0.5 ml) and different ratio of glutaraldehyde [2; 2.5; 5; 7.5; 10] was mixed and polymerized at 40°C for 90 min. After that time the hydrogel samples were ready to use. All samples were washed in excess water to remove unreacted components. In this study, all of the samples were gelated 100% and no extractable monomers were observed.

2.3. Swelling properties

For testing pH dependent of hydrogels, all hydrogel samples were equilibrated in 2 ml 0.1 M buffer solutions [acetate pH 4.5; P_i (phosphate) pH 7- 7.5], 0.1 M HCl and 0.1 M NaOH solutions at 37°C. The time intervals are 5 min - 10 min - 30 min - 1 h - all day. The gravimetric method was used to determine the swelling ratio of hydrogels. The swelling ratio was calculated according to Eq. (1).

$$SR\ \% = [(w_S - w_D) / w_D] * 100 \quad (1)$$

Where w_D and w_S are dry and wet weights of hydrogels, respectively. All experiments were repeated triplicate, and the calculated swelling ratios were the average of these three experiments.

2.4. Insulin loading and release experiments of hydrogels

In this study pre-mixed insulin solution was used (purchased from pharmacy). The pH of this insulin was adjusted pH 7 by adding P_i buffer. Before the insulin loading, the dried acrylamide-based hydrogels (ACR/CMC and ACR/Chi) and Chi/glutaraldehyde hydrogel were pulverized. The dried particles were equilibrated in insulin solution (20 mg 5 ml^{-1}) (which was adjusted to pH 7 with Pi buffer) for 30 min at 37°C. Also, the same procedure was repeated for Chi/glutaraldehyde hydrogel for insulin loading (only the best hydrogel composition).

The hydrogels were washed with water to remove excess insulin. The amount of insulin released was measured spectrophotometrically at a wavelength of 276 nm. All of the insulin loaded hydrogels were stand up 5 mM glucose solution. The glucose solutions were prepared in stimulated gastric fluid (pH 1.2) and intestinal fluid (pH 7.2).

The changing of glucose was determined by DNS method. DNS method was done according to Miller.[21] Briefly; an aliquot of the glucose solution (0.5 ml) and 0.5 ml of the DNS reagent was added to the test tube and the mixture was incubated in a boiling water bath for 5 min. After cooling to room temperature, the absorbance of the supernatant was measured at 540 nm.

3. RESULTS AND DISCUSSION

Nowadays, the oral insulin therapeutic hydrogels are very attractive and good alternative for diagnosis of diabetes. 3D crosslinked polymer structures as known hydrogels can be the best alternatives. They absorb large amounts of water that is the most important property for oral delivery therapeutics. It means that the polymer can swell and the therapeutics can be released into fluid. Many factors can affect the structure and their swelling such as charge, concentration, hydrophobic/ hydrophilic balance, cross-link density. One of the examples of the charge effect is acidic solutions of Chi. Acidic solutions of Chi when exposed to alkaline pH result in a decrease of the apparent charge density of the polymer, and thereby in the formation of physical gels due to hydrogen bonding and hydrophobic interactions. To obtain CS-based homogeneous hydrogels or porous materials with chemical stability at pH < 5.5, CS has been cross-linked by glutaraldehyde (GA), epichlorohydrin (ECH), and so on.[19,20] In this study, we aimed to modulate the mechanical properties, the water content of hydrogels, the response to an external stimulus, and also to design chelating performances, composite hydrogels.

3.1. Acrylamide based hydrogels

The different requirements for oral hydrogels for using clinical approach are existed, and these are biocompability/nontoxicity, mechanical properties, viscosity, stability and biodegradability.

As known, if acrylamide is used large amount or alone, it can be cancerogenic. Herein, to overcome this problem, the hydrogels were prepared with biocompatible and semi-natural comonomers (CMC and chitosan). CMC which is derivative of cellulose is widely used in pharmaceutical industry as emulsifier, viscosity modifier and stabilizer to develop different pharmaceutical dosage form. CMC is semi-natural polymer and has excellent water absorbing and swelling capacities. It is physiologically non-toxic and compatible with mucous membrane, bone and skin.[18] The ACR based hydrogels were formed by chemical crosslinking for better mechanical properties and long term stability in different medium conditions. The usage of toxic crosslinkers can be dangerous while preparing hydrogels, but all of the washing solutions and the stability tests show that any excess component is not

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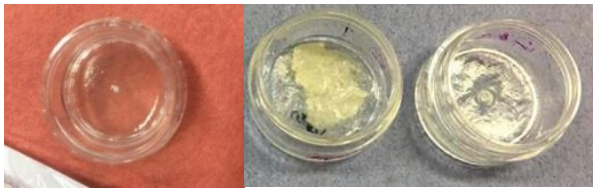
exist. The swelling test (especially 24 h) results of hydrogels can be seen in Figure 1. These results showed that hydrogel was not dissolved totally and could not accumulated in the body as stated in the papers.[18-20]



(a) (b)

Figure 1. Photos of hydrogels: a) Dried hydrogel, b) Swelled insulin-loaded hydrogels.

CMC is used to prevent postoperative adherences and epidural scarring. CMC is also degraded by cellulolytic enzymes which is found intestinal fluid. There are some different models for *in vivo* analysis. Cell culture models are suitable to study acute, delayed and repeated toxicity. Also, parallel artificial membrane permeability assay (PAMPA) and CaCo-2 cell systems can be studied. While PAMPA is used to evaluate passive permeability, the CaCo-2 cell systems are used to measure passive and active permeability. CaCo-2 cells allow to simultaneously evaluate efficacy and safety of delivery systems, investigating their action mode. We will planning to study cell culture assays of our hydrogels the future, but in this study, our only aim is to make the best promising hydrogel as insulin nanocarrier.

3.2. Chitosan based hydrogels

In most of the oral delivery system, chitosan is used because of its biodegradability, low toxicity, modifying with different chemicals. By this way, many different alternative gels can be prepared effectively.[17,23] The main problem is synthesized chitosan hydrogels which have poor mechanical strength and stability. To overcome this problem, glutaraldehyde is used as crosslinker but it can be accumulated in the body if used excess amount.[18] In our study, the 2.5 (v/v) % glutaraldehyde was chosen.

3.3. pH responsive and swelling characteristics of hydrogels

The pH sensitivity of hydrogels usually depends to acidic and basic groups in the structure. The charge and ionization state of the groups can be changed according to the pH of the medium. As seen in Table 1, ACR/CMC and ACR/Chi hydrogels can be stable at all acidic pHs (HCl pH 1 and acetate buffer pH 4.5). Chi/Glutaraldehyde hydrogels were affected after 10 min in all acidic solutions. As known, chitosan hydrogels swell at acidic pHs and the structure of chitosan hydrogels can be deformed in basic solutions. This may be due to the reactive groups at the surface of chitosan hydrogels. The deprotonation structure on the surface of chitosan increased, ionic interactions in the medium changed and this situation may lead to the decrease of the crosslinking followed by increased swelling.

P_i buffer studies of all hydrogels are very important. These results are the clues of the behavior of hydrogels for insulin delivery system in body fluids. ACR/CMC and Chi/glutaraldehyde hydrogels started to swell after 30 min. This could be a good result and showed that they could be alternative materials for delivery of insulin. However, ACR/Chi hydrogels were very stable and rigid and it is a big problem for releasing of insulin.

Insulin has to be released in small intestine at 0-30 min range. After that time, insulin releasing can be resulted by hypoglycemia. The composition of ACR/CMC hydrogels can change the results. Because, CMC has excellent water adsorption and can swell at different ratios according to medium conditions. The mechanical strength is more than many other biopolymers used in pharmaceutical field. The less amount of CMC can be a problem for swelling.

The swelling characteristics of hydrogels mostly depend on the hydrophilic network. The water or buffer solutions migrate into the network and can change the hydrogel structure. The swelling ratio of ACR/CMC hydrogels was 80 % after 1 h, the reason of these result is due to the carboxyl groups of CMCs ionized at pH 4.5 and above. But these ionic changes did not affect the hydrogels structure too much. ACR/Chi hydrogels swell 400% and this shows that it can be a good alternative only in short time period (0-10 min).

3.4. *In vitro* release study of insulin

The insulin was loaded on all of the hydrogels. ACR/CMC hydrogel (1:0.01) showed best results. The particles were loaded in the range of 45-65%. Insulin molecules tend to polar groups and can make hydrogen bonds. More acidic or carboxyl groups provides more hydrogen bonds at low pH (acetate buffer). The release of insulin is nearly 45%. At pH 1 (HCl solution), the effective pore size of the hydrogel decreased and the insulin entrapped inside hydrogel. At pH 7, ACR/CMC hydrogels released 65% of insülin.[25]

In vitro release of insulin depends on many factors. An initial release of the hydrogels was more than expected. Because some of the insulin molecules could be adsorbed toward the structure of the hydrogel and this caused rapid releasing. At pH 7, 65% of insulin was released from ACR/CMC hydrogels within 30 min and

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remaining insulin was released up within 1 h. At pH 4.5, most of the carboxylic groups of the hydrogel were ionized so that 60% of insulin released within 10 min and remaining insulin released up within 30 min. The reason may be that the swelling rate of the hydrogel at pH 4.5 is more than pH 7. These results show that the ACR/CMC hydrogel structure, reactive groups of the hydrogel and swelling properties are pH sensitive.

ACR/Chi and Chi/ glutaraldehyde hydrogels released 85% of insulin within 5-10 min and released the remaining within 30 min. The reason of this rapid releasing can be the amount of insulin which is too high for these hydrogels (the pore structure can be small) and there is not also ionized groups for hydrogen bonding with insülin.[26]

Table 1. The swelling behavior of hydrogels in buffer and solutions (NaOH, HCl)

Hydrogel	Buffer/ Solution (0.1M)	5 min.	10 min.	30 min.	1 h.	24 h
ACR/ CMC	Acetate (pH 4.5)	+++	+++	+++	+++	++
	P_i (pH 7)	+++	+++	+++	+++	+++
	P_i (pH 7.5)	+++	+++	++	++	++
	NaOH	+++	+++	+++	++	++
	HCl	+++	+++	+++	++	++
ACR/ Chi	Acetate (pH 4.5)	+++	++	++	-	-
	P_i (pH 7)	+++	++	++	-	-
	P_i (pH 7.5)	+++	++	++	-	-
	NaOH	+++	++	++	-	-
	HCl	+++	+++	++	-	-
Chi/glutaraldehyde	Acetate (pH 4.5)	+++	++	++	+	+
	P_i (pH 7)	+++	++	++	+	+
	P_i (pH 7.5)	+++	++	++	+	+
	NaOH	+++	++	++	+	--
	HCl	+++	++	++	--	--

+++ : stabile, ++ : partially swelled, + : swelled, - : not gellated

As a result, it can be said that the ACR/CMC hydrogels can be good, low toxicity, biocompatible alternative for insulin deliver

4. CONCLUSIONS

The ACR/CMC and ACR/Chi hydrogels were synthesized by free radical polymerization. This may leads to the mechanical strengths of these hydrogels. ACR/CMC, ACR/Chi and Chi/glutaraldehyde hydrogels showed pH sensitivite properties. The pH behavior and the insulin releasing results showed that ACR/CMC hydrogels could be used in biomedical approaches especially biomolecule delivery systems. In our study, the hydrogel was prepared with CMC as a comonomer and also for biocompability. This is the first time for therapeutic hydrogel preparing with ACR/CMC. The results of insulin releasing showed that ACR/CMC hydrogels could be a good and new alternative for delivery at small intestine. This study is a preliminary work for the therapeutic hydrogels with ACR/CMC for biomolecule delivery.

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Conflict of interests

Authors declare that there is no a conflict of interest with any person, institute, company, etc.

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