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Preparation of Serum Albumin Loaded Injectable Silica-Gel Matrix

Ihsan COSKUN, Nursu ERDOGAN
Biomedical Engineering
İzmir Katip Çelebi University
İzmir, TURKEY
ihsancskn96@gmail.com, nursuerdogann@gmail.com

Didem ŞEN KARAMAN*, Ozan KARAMAN
Biomedical Engineering
İzmir Katip Çelebi University
İzmir, TURKEY
didem.sen.karaman@ikc.edu.tr, ozan.karaman@ikc.edu.tr
*Corresponding Author

***Abstract*— Biomolecules play an active role in tissue regeneration. It is suggested that these biomolecules can be more efficient once the delivery is provided locally in the meant of with the local drug delivery systems. In the literature, the use of silicon dioxide gel matrix as a drug delivery system for different therapeutic agents are presented. The aim of this study is to prepare a silica gel drug delivery system that can be used as a bioactive molecule delivery system and to investigate the release profile of biomolecules by considering the biocompatibility of silica gel matrices and their positive effects on tissue regeneration. The methods intended to be followed to accomplish the stated objectives are to produce biocompatible silicon dioxide gel matrix by sol-gel method and to characterize the resulting silica gel matrices by testing both chemical content and physical properties and injectability. The release profile of BSA (Bovine Serum Albumin) protein from silica matrices as biomolecules is determined from optimized silica gel matrices. In this study, it was found that silica gel matrices are capable of delivering effective biomolecules and providing a sustained drug release profile.**

Keywords — silica gel matrix, sol-gel method, drug delivery systems

I. INTRODUCTION

Drug delivery is accomplished for many decades through various approaches including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols, and injectables to treat diseases. Drug delivery systems can be grouped as systemic drug delivery and local drug delivery. Systemic drug delivery is included oral, rectal and sublingual routes on the side local drug delivery can be expressed as ocular, transdermal, mucosal, and pulmonary.

However, some difficulties of systemic drug delivery such as undesired side effects or toxic effects, long circulation time into the circulatory system, rapid clearance by kidney and liver which cause lower dosage on the damaged area than needed lead researchers to develop more effective systems for drug delivery. With the aid of advances in material preparation technology the control of drug's release and delivery at the desired side of the body can be provided [1].

Sustained release and controlled release are used two terms in drug delivery. Sustained-release retains the release of therapeutic agents thus delayed and prolonged drug existence in the circulation. On the other hand, term-controlled degradation means prevention of sustained drug action. Furthermore, release of drug ingredients from controlled release drug delivery systems improves predictable and reproducible [2].

Gels are semisolid structures planned for application on local drug delivery systems or reachable mucous membrane. They are consisting of colloidal particles which are distributed in dispersion medium or solvent forming a three-dimensional matrix. Gel matrix has been used in different areas in medicine such as healing of joint, regenerate bone, repair tissue and organs, biosensors. Many structures usage is defined for gel and gel matrix such as hydrogels, xerogels, aerogels, and cryogels [3-5].

Generally, various polymers are used for the preparation of gels to provide structural strength, improve the adherence, and decrease the degredation of large molecules. In most cases, optimization for polymer concentration is required because of the significance of viscosity that gel has. Sol-gel matrix processing has been advantages including low – temperature processing, ease of fabrication, gelling network, high surface area, chemical control and controlled release [6-7].

Silicon and derivatives have been characterized by special properties combining biocompatibility and bio-durability so it is using in medical application. Other advantages are low surface tension, chemical, and thermal stability.

Silica gel matrixes have remarkable potential for controlled and local drug release and delivery. They enhance the osteoblast formation and increased the collagen formation in soft and bone tissue [8]. Sol-gel processed SiO_2 bio-matrix has vascularization potential and simple integration within the tissue for rats [9].

The aim of this study is to provide injectable drug delivery system considering the biocompatibility of silica gel matrices prepared by sol-gel method and the elimination of the first- pass effect of bioactive molecules using the strategy of local drug delivery. Development of drug delivery systems for regenerative medicine optimized for bioactive molecule delivery.

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II. MATERIALS AND METHODS

A. Preparation of Silica Matrix

Different H_2O/TEOS (tetraethyl orthosilicate) mole ratios (R) which are 10, 20, 30 and pH, aging times were used to prepare gel matrices. The initial pH of all sol adjusted to 2 with pH meter. The TEOS was added and stirred at room temperature and 290 rpm for 30 minutes. Then pH was increased to three different parameters these are 5, 6 and 7 slowly and the solution stirred for 30 minutes. After the hydrolysis, the sols were aged at 4 C° for different time periods which are 24, 48 and 72 hours.

B. Preparation of BSA Silica Matrix / HPMC Material

Firstly, the sol-gel method was used for the preparation of the new matrix by acid-catalyzed hydrolysis. During the sol-gel approach HPMC (hydroxypropyl methylcellulose) was added to matrix to provide the adhesiveness for the gel matrix. 178 mg HPMC was dissolved in 6.25 ml H2O for 24 h and at 40 C°, 260 rpm. After dissolution H_2O / HPMC solution, then medium pH was set to 2. To constitute silica matrix / HPMC, adding 2.5 ml TEOS and stirred 30 minutes. After that, pH of solution was adjusted to between 4-5 before BSA loading. BSA loading was applied to the silica matrices formed and BSA rates are 5%, 10%, %20. These percentages are BSA mass ratio to all gels mass. Finally, increased the final pH is 6 and silica matrix / HPMC aged at 4 C° for 24 hours.

C. BSA Release Analysis

During the investigation of BSA release SBF (simulated body fluid) media was used and SBF was prepared for BSA releasing. The SBF solution was prepared by dissolving sodium chloride, potassium chloride, sodium hydrogen carbonate ($NaHCO_3$), di-potassium hydrogen phosphate trihydrate ($K_2HPO_4.3H_2O$), magnesium chloride hexahydrate ($MgCl_2.6H_2O$), calcium chloride ($CaCl_2$), sodium sulfate (Na_2SO_4) and Tris-hydroxymethyl aminomethane ($(HOCH_2)_3CNH_2$) in deionized water. All reagents must dissolve one by one and dissolve a reagent only after the preceding one is completely dissolved. Release analysis from silica matrices on which BSA was loaded was performed a pH 7.4 and 27 °C (room temperature) SBF solution. The concentration of silica matrices over BSA concentrations was kept as 20 mg / mL. The prepared solutions were carried out at a temperature of 37 °C in the shaker and at 150 rpm speeds for different time intervals (15 min, 30 min, 1h, 2h, 4h, 6h). BSA release from the gel matrices was determined with Nanodrop Spectrophotometer at 280 nm.

D. Silica Gel Matrix Injectable Test

The injectability of the produced gel matrices was investigated and different parameters were determined, the experimental groups were formed. They are HPMC – without HPMC matrices and aging processes at 4 ° C in fridge and 27 ° C (room temperature) under vacuum. In literature, the average of pushing force for thumb finger is 100 N approximately [10]. Silica - gel matrixes of different properties were put into the syringe and injectable capabilities were observed when 50 N was applied each sample for replacement of 1 cm with 6 mm/sec velocity. Four different gel matrixes were loaded and the amounts of matrixes in syringes were determined. After applying 50 N forces in 1 cm, adjusted the amounts of output gel matrix. As final step, ratio of amounts output gel matrix to amount initial gel matrix was calculated.

III. RESULTS

The three R values have been an important role for consistency of silica gel matrix in three different pH values are compares these values, R=30 value has been found closest to the cream or gel consistency and simple structure. Because of TEOS has been required more independent OH− ions. Therefore, finding the optimum silica gel matrix, R-value has been determined as 30. Solvent evaporation has been affected to consistence and whole structure for silica gel matrixes. It can be seen at different aging times. This situation has been created distributed structure, fragile and more solid matrices when compared the aged time periods so aged time should be 24 h to get the optimum matrices. The gelling form has occurred in condensation reactions which have been provided connection between silanol groups. Condensation reactions have been performed at three different pH values. Compared pH values which increased values gel matrices gone to more solid and brittle structure. Condensation pH value 6 was the most available to obtain the semi-solid structure and for jelly consistency. Visual observation and interpretation for each sample were made in the following table for the prepared samples of given Figure 1. According the visual inspections B1 and B2 numbered samples were chosen for the future of the study.

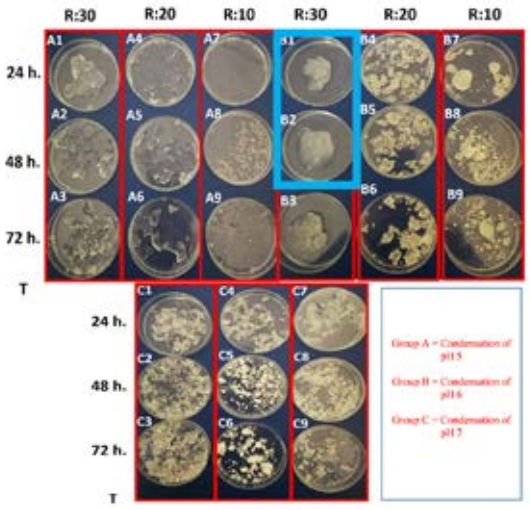

Figure. 1. Image of Gel Matrices

The impact of storage conditions in the means of fulfillment the condensation process was evaluated with the in-lab injection test set-up. It has the ability to pass through injection in four different samples in Table 1. Due to the material used and the different environmental conditions, the amount of injection is changed. At a rate of 6 mm /sec, a force of 50 N was applied to

pass through the maximum amount of HPMC gel matrices dried at room temperature and under vacuum at the same time.

Due to the increased adhesion of the HPMC, a large amount of gel was passed when the same force was applied to the compact structure. The effect of *in vacuo* condition has been used eliminate the space in gel matrix so force delivered without loss when applying to the force gel matrices and vacuum could prohibit the formation of micro cracks and reduced the shrinkage of the samples.

Table I. Applied the Forces Percentage of Passing Gels from Injection

Types of Gel	Percentage of Passing Gels from Injection
HPMC Gel Matrix at 4 □	26.76 %
Without - HPMC Gel Matrix at 4 □	06.66 %
HPMC Gel Matrix at 27 □ and Vacuum	34.37 %
Without - HPMC Gel Matrix at 27 □ and Vacuum	23.80 %

The biomolecule release with the optimal gel matrix was very effective like burst release and sustained release. As BSA biomolecules have been burst release in 5 % biomolecule loaded gel matrices, BSA have been sustained release in 10 % and 20 % loaded gel matrices in Figure 2.

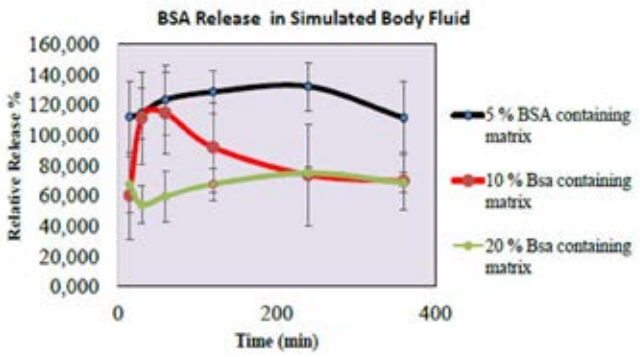

Figure. 2. BSA Release in Simulated Body Fluid

If burst release is needed, gel matrix has been contained low concentration biomolecule on the other hand to provide sustained release, high concentration of biomolecules should be present in gel matrix. As a result, depending on the application of the gel matrices was obtained, drug concentration can be changed and gel matrices respond to this concentration and can be released and the gel matrix release profile approaches the zero-order release profile. Zero-order release, in which a drug has been released at a constant rate, was the ultimate goal of all controlled-release drug-delivery mechanisms. Zero-order or constant rate release of drug is desirable in order to minimize alterations in drug concentration in release enviroment. Such excursions, which may lead to periods of under exposure or overexposure, are particularly likely to occur for drugs that are rapidly absorbed and rapidly eliminated.

IV. CONCLUSION

In this study, TEOS and HPMC are used together to get optimum silica gel matrices. First, condensation of pH, R value and aging period time have been found to be optimized and found as for respectively pH= 6, R= 30 and 24 h incubation under vacuum at room temperatures. HPMC was used to increase adhesive properties and this effect was observed in injectable test and visual inspection with creamy look of gel matrix. It was observed the removal of air bubbles content with the aid of vacuum environment at room temperature yield better injectable, silica – gel matrices. Also, when gel matrix was loaded with low starting concentration (5% with respect to total content) with BSA, it has provided burst release profile whereas increment of the BSA content (10, 20 %) lead the sustained drug release. It can be revealed as the silica gel matrix could be used biomolecule reservoir for different concentrations to provide immediate release and sustained release profiles. In the future of the study we aim to provide cytotoxicity inspections with the obtained matrices and also revisit the formulation by integration of different biomolecules (such different peptides or proteins) that could promote the regeneration of bone tissues.

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