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Preparation and Application of Biocompatible Carrier Implant to be Used in the Controlled Acquisition of Digoxin

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Abstract: In this study, a persistent system is aimed to be established which contributes to slow basal digoxin release in the treatment of cardiac failure. Poly(2-hydroxyethyl-metacrylate-methylmetacrylate) (p(HEMA-MMA) copolymer that can swell by taking on water is prepared in cylindirical form by UV photopolymerization method for the controlled-release of digoxin and effective hydrogel implant formulation. A batch of p(HEMA-MMA) composition is prepared in different monomer ratios. Biocompatibility is improved by adding PEO, PEG and serum albumin to the structures of p(HEMA-MMA), respectively. Scanning electron microscope (SEM) studies are carried out for the surface structure of the prepared carrier implant material and differential scanning calorimetry (DSC) studies for the thermal stability analysis. Swelling behaviors are investigated by transferring solvent molecules to the hydrogels. Digoxin release kinetics are evaluated by applying three different accumulative digoxin doses (100, 250 and 500 U/mL) in the persistent flow release system containing physiological phosphate. Power law, level-zero, and Higuchi model equations are utilized so as to evaluate the release mechanism of digoxin. The most suitable results are acquired from the composition whose HEMA:MMA monomer ratio is 1:0.5 (v/v) in drug accumulation and release studies. It is observed from the SEM image that the carrier implant in the structure of the acquired hydrogel has a smooth surface. According to DSC results, it is seen that thermal stability decreases in the event that MMA comonomer is added to the structure of the pHEMA hydrogel. Balance water amount within the physiological phosphate buffer of the p(HEMA-MMA) copolymer is observed to be less than the pHEMA. Digoxin release loaded to carrier implants by different ratios takes a long-term period as expected. It is decided that the formulation established in the study can be successfully applied for the basal digoxin level over four weeks in the treatment of chronic cardiac failure.

Keywords: pHEMA; p[HEMA-MMA]; carrier implant; digoxin; controlled-release.**Submitted:** September 21, 2016. **Revised:** September 30, 2016. **Accepted:** December 20, 2016.

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INTRODUCTION

Cardiac failure is a complex clinical syndrome with labored breathing, fatigue, and exercise intolerance because of impaired blood pumping or ventricular filling due to functional and anatomical disfunction. Cardiac failure is an important clinical issue that results in cardiovascular mortality and morbidity throughout the world. There have been at least 15 million patients with cardiac failure and a similar number of patients with asymptomatic ventricular disfunction in countries, which are the members of the European Society of Cardiology [ESC]. The cardiac failure prevalence is between 2-3% and the rate is significantly higher in elderly patients above 75 year-old [1].

A single extended prospective study has been carried out by applying digoxin to the patients of cardiac failure [2]. In this Digitalis Investigation Group's study, 6800 patients with (New York Heart Association) NYHA II-IV functional capacity are treated with randomized placebo; however, no positive effect was observed in terms of mortality.

Controlled release method is designed to release the active substance into the system at desired intervals by a specified rate in the required quantity. In the field of biomedical [medicine] studies, the main target is to minimize the drug dosage along with extending the dosing interval and increasing the quality of life while not causing any side effects on the patient. Controlled release systems are best options to meet these expectations. When the polymer [natural or synthetic] utilized in the controlled drug release is used along with the drug, the active substance is released as determined in advance. As reported by many researchers, the fact that toxic effects have been minimized thanks to the controlled release system and no continuous daily-usage is required providing convenience for the patients.

The materials with high biocompatibility are used in the formation of the devices that can be placed within the body. However, the studies are being carried out due to the fact that no material with the perfect biocompatibility has been created yet [3]. Hydrogels, which are insoluble in water, can absorb water at least 20% more than the dry mass, cross-linked, three-dimensional, hydrophilic and polymeric structures with high mechanical stability.

A hydrogel used in medical applications widely is cross-linked pHEMA. It is similar to the natural tissues because of the water content. It is inert in normal biological reactions. It is resistant to degradation, is not absorbed by the body, can be sterilized with heat, and can be prepared in many different shapes and forms [4-6]. The other hydrogel has the

medical importance is polyacrylamide. In addition to HEMA and acrylamide monomers, N-vinyl-2-pyrrolidone [NVP], metacrylic acid [MAA], methyl methacrylate [MMA], and maleic anhydride [MAH] are often found in medical hydrogel formulations. In addition, hydrogels may be combined with various ingredients in order to gain the desired properties. Acrylate origin polymers are long-lasting synthetic polymers. Poly[methyl methacrylate] [pMMA] placed in this group is used in numerous applications in biomedical and biotechnological fields as it is a biocompatible synthetic polymer.

The aim of this study is to develop a biologically compatible [pHEMA] materials of hydrogel-origin that can be used as biomaterial in the controlled drug release system. The amount of the released insulin is measured by applying digoxin with different dosages to the carrier implant material with hydrogel structure.

MATERIALS AND METHODS

2-Hydroxyethyl methacrylate [HEMA], methyl methacrylate [MMA], N,N-methylene bisacrylamide, polyethylene glycol [PEG], polyethylene oxide [PEO], and N,N-azobisisobutyronitrile [AIBN] were obtained from Sigma-Aldrich Chemie GmbH [Germany]. Human serum albumin, fibrinogen, γ-globulin, and bovine serum albumin were obtained from Sigma-Aldrich. All other chemicals in analytical grade were obtained from Merck AG [Wuppertal, Germany]. Distilled water used in each phase of the study were obtained from Mp Minipure Super Auto [Mes Medical, Turkey] brand ultra-pure water system.

Synthesis of Biomaterials

The polymerization mixture prepared with HEMA and MMA monomers were used as monomers in a ratio of 1:0-0:1 [v/v], N, N-methylene bisacrylamide as cross-linker, [BSA] [10 mg], and ammonium persulfate [AMP] as launcher [5 mg] and 5 mg of human serum albumin [HSA]. 10 mg of polyethylene glycol [PEG] or polyethylene oxide [PEO] was added to the structure to improve the biocompatibility property of carrier implant will be synthesized and nitrogen gas was passed through polymer solution for 2 minutes.

10% Tetramethylethylenediamine [TEMED] as accelerator was added to the polymerization mixture, passed nitrogen gas for the duration of 1 minute, poured into cylinder molds with diameter of 0.5 cm and 5 cm in length and it was synthesized at room temperature by UV light photopolymerization method. Different amounts of digoxin loading of polymeric carrier biomaterial to be used in controlled drug oscillation system were introduced by UV light-induced photo-polymerization method under the same

conditions as given above. Cylindrical polymeric carriers formed because of polymerization, they were washed with distilled water and were stored at 4 °C until use. The composite membranes that pHEMA-based hydrogel were synthesized by UV photo-polymerization method [5]. Human serum albumine (HSA) and polyethylene glycol (PEG) was added to the structure to achieve biocompatibility of pHEMA and p[HEMA-MMA] hydrogel synthesized in the controlled oscillation system and targeted efficient dosage in the drug oscillation system.

Characterization of Biomaterial

Designed systems for the controlled release of biologically active proteins, hormones, or drugs should have suitable surface morphology. The surface area is one of the important factors that determines the rate of drug oscillation [7]. It is known that the drug oscillation rate is quite low in the system that developed with non-porous biomaterials.

The scanning electron micrographs of the carrier systems were determined with JOEL brand apparatus and the thickness in the wet state of p[HEMA-MMA] membrane with a digital caliper to examine the surface morphology of the oscillation of the system that we developed in our study.

The density of hydrogel cylinder in shape determined with pycnometer by using [n-decane] non-solvent liquid for membranes. The mechanical strength of carrier implant, pHEMA and p[HEMA-MMA], were determined by DSC [Model DSC-60-DTG-60H, Shimadzu, Japan] analysis. The swelling property of biomaterial in hydrogel structure was determined by gravimetric method in salt solution [0.85%, NaCl] at room temperature in a buffer system [pH 4.5-8.5]. Firstly, examples were placed in an inflatable media, then the balance environment was changed. The swelling ratio of the biomaterial was calculated using the following equation.

$$\% \text{ Equilibrium water content [w/w]} = [(Wd - Wk)/Wk] \times 100 \qquad (\textbf{Eq. 1})$$

Here Wk, dry hydrogel weight; Wd, weight of hydrogel reached balance of water content.

Contact Angle and Surface Free Energy

The measurements of the contact angle in our study were carried out for the determination of carrier implant surface polarity since important results about the interaction with micro-environment of biomaterials can be determined by investigating the wettability properties. Left and right contact angles and drop size parameters on the surface of the polymer by creating a drop with the help of a micro-syringe were

calculated automatically from the digital image. Wettability with a liquid of solid surface and contact angle concept [θ], have been formulated for the first time by Young [8]. There is not a single agreed approach for the determination of the surface energy [sometimes is defined as solid surface tension] from contact angle data [9]. These results are analyzed according to four methods [10, 11]. These are; Zisman's critical surface tension, Fowkes' geometric expression, Wu's harmonic expression and van Oss' acid- base approach. The contact angle was calculated by using the formula created by the Young and solid surface tension is calculated with the four methods given above separately.

Adsorption of Serum Protein

pHEMA and P[HEMA-MMA], to determine the blood compatibility of biomaterials, was transferred into the human blood serum diluted phosphate buffer [7.5 ml, 50 mm, pH 7.4] at a rate of 1/5 and stirred for 120 minutes at 37 °C. The adsorption of serum proteins was studied in a batch system. It was performed for each protein with a specific initial concentration. It was determined the amount of protein adsorbed to the carrier implant by using fluorescence spectrophotometer [Jasco FP-750, Tokyo, Japan] [6].

Blood Compatibility Analysis

The carrier implants, pHEMA, p[HEMA-MMA], cut 0.5 cm long and was brought to equilibrium in 0.85% NaCl solution. A sample of venous blood from a healthy person was mixed with sodium citrate in a 1/9 ratio and 10 minutes, centrifuged at 3000 rpm, and the plasma was obtained. 300 µL of plasma with sodium citrate was contacted with the polymer tubes and were incubated for 1 hour. Plasma did not make contact with the polymer used as a control.

***In vitro* Oscillation Studies**

Digoxin is loaded to investigate the controlled release of digoxin to carrier support material by prepared arrest method in the matrix. Biomaterials loaded with digoxin are placed into a continuous system reactor and supplied to enter the physiologic buffer solution at a constant flow rate by a peristaltic pump [Ismatec, model IPG, Germany]. The amount of the released drug was determined by spectrophotometry [Shimadzu, Model 1601, Japan] at a wavelength of 450 nm at certain intervals.

Oscillation Mechanism of Digoxin from the Biocompatible Carrier Implant

The oscillation with diffusion from swelling hydrogels of the active substance is defined in the best way by act of Stefan-Maxwell or Fick [12].

$$J = - D \, dC_m/dx \qquad (\textbf{Eq. 2})$$

In this equation, J shows the release from the membrane of the active substance in the direction of decreasing concentration; $g.cm^{-2}$ / sec [quantity/surface. time]; D is the diffusion coefficient of the active substance which diffuses through the membrane; cm^2 / sec [space/time] and dC_m / dx are the change of the drug concentration in the membrane in the x distance.

Another empiric equation that is used to explain the release mechanism in the controlled release system is equation developed by Peppas and colleagues assuming that function depends on time [13].

$$M_t / M_\infty = k \, t^n \qquad (\textbf{Eq. 3})$$

In this equation, M_t shows the amount of molecules released at t time; M_∞ is the amount of the remaining oscillating molecules in the environment; k is the structural/geometric constant for the particular system and n is the release mechanism.

Initially, the ingredient is dispersed and dissolved in the carrier implant. The effective oscillation in the polymeric materials that is used as the carrier implant in the controlled drug oscillation system characterized by Fick, non -Fick [abnormal], Case II, or super case II depending on the temperature and thermodynamic behavior of the system.

The mathematical modeling widely used for the investigation of drug oscillation kinetics in controlled drug oscillation system is the first degree equality [$D_t = k_o \, t$] in [13]. In this equation D_t shows the mass of the drug released instantly t; k_o is the emission rate constant at the first degree.

Another kinetic equation is the Law of Strength that is used in the elucidation of oscillation mechanism in controlled drug oscillation systems [$M_t = M_\alpha \, k_p \, t^n$] [14, 15]. In this equation, M_t shows the mass of released drug; M_α is the mass of the released drug to reach at the balance time; k_p is the kinetic constant of the law and n is the component of oscillation.

Higuchi's equation is used for diffusion-controlled release of drugs from insoluble and biologically without degradation matrix. It is used the different formulations of Higuchi's equation depending on conditions such as homogeneous or heterogeneous matrix and the geometry of the matrix [16].

$$Q = [DC\,[2A-C]t]^{1/2} \quad \Rightarrow \quad Q = k_H\, t^{1/2} \qquad (\textbf{Eq. 4})$$

In the equation, Q shows the drug dose emitted per unit surface area at instantly t [mg cm^{-2}]; D is the diffusion coefficient of the substance in the matrix [cm^2 $time^{-1}$]; C is the solubility of the substance in the matrix [mg cm^{-3}]; A is the amount for per unit volume that is loaded initially [mg]; t, time [day]; k_H is the Hugichi's oscillation speed constant [mg cm^{-2} $t^{1/2}$].

RESULTS AND DISCUSSION

Results

Findings of the present study showed that the mechanical power of the membrane of p(HEMA-MMA), a synthetic polymer, varies depending on the ratio of the comonomer (Table 1). Since the hydrogel composition of p(HEMA-MMA) at a monomer ratio of 1:1 had sufficient mechanical strength; this ratio was used for further steps of the study.

Table 1: Effect of the composition of membrane preparation to the mechanical strength of composite hydrogel synthesized in different MMA rates.

HEMA:MMA ratio [v/v]	Polymerization	Mechanical strength
A] 1.00:0.00	+	Medium
B] 1.00:0.25	+	Medium
C] 1.00:0.50	+	Enough
D] 1.00:1.00	+	Enough
E] 0.00:1.00	-	Inadequate
F] 0.25:1.0	-	Inadequate
G] 0.5:1.0	-	Inadequate

Using a digital calliper, the thickness of the wet hydrogel was recorded as 2.70 mm. Hydrogel's density was found to be 1.10 g/cm^3 by using a non-solvent fluid for the material (n-decane) with the aid of Gay-Lussac pycnometry.

The composite hydrogel, dried in a vacuum incubator at a temperature of 30 °C, was covered with gold while being kept under reduced pressure and scanning electron microscopy of the membranes was performed to confirm the hydrogel had a smooth surface (Figure-1).

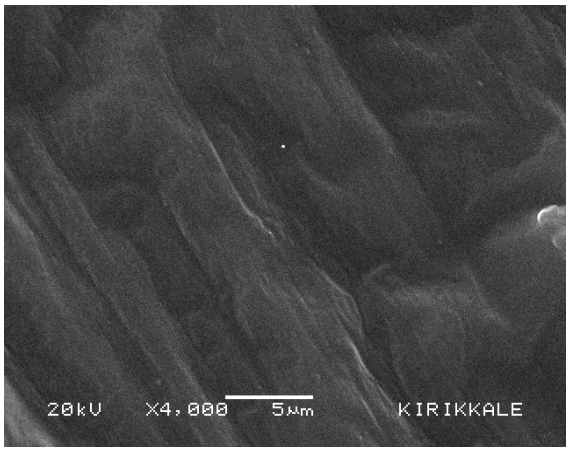

Figure 1: SEM image of the carrier implant used in the controlled oscillation system.

Figures 2 and 3 show the balanced inflation percentage under different medium buffer systems at 25 °C of pHEMA and p(HEMA-MMA) hydrogels prepared to be used for digoxin release.

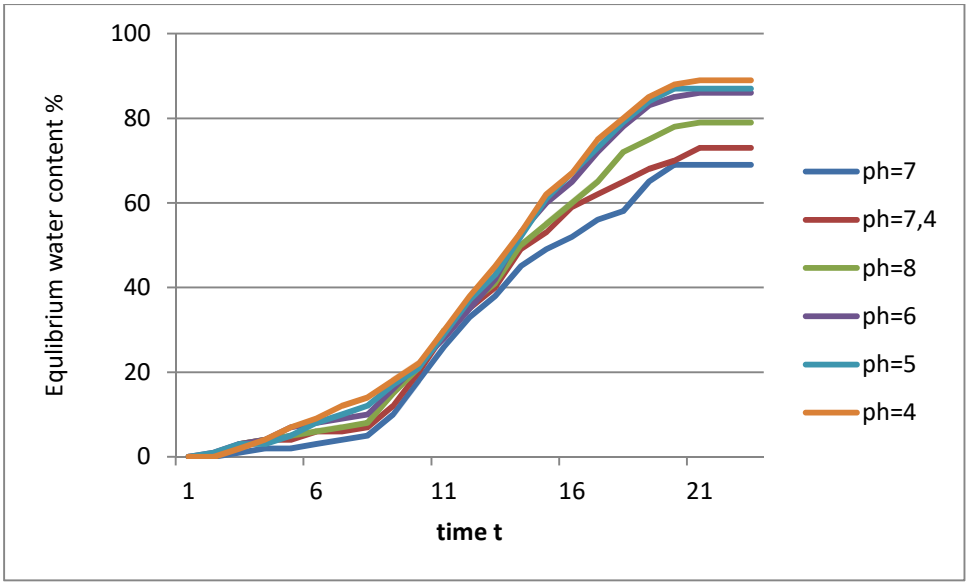

Figure 2: The swelling behavior of pHEMA hydrogel in different buffer systems (t = hours).

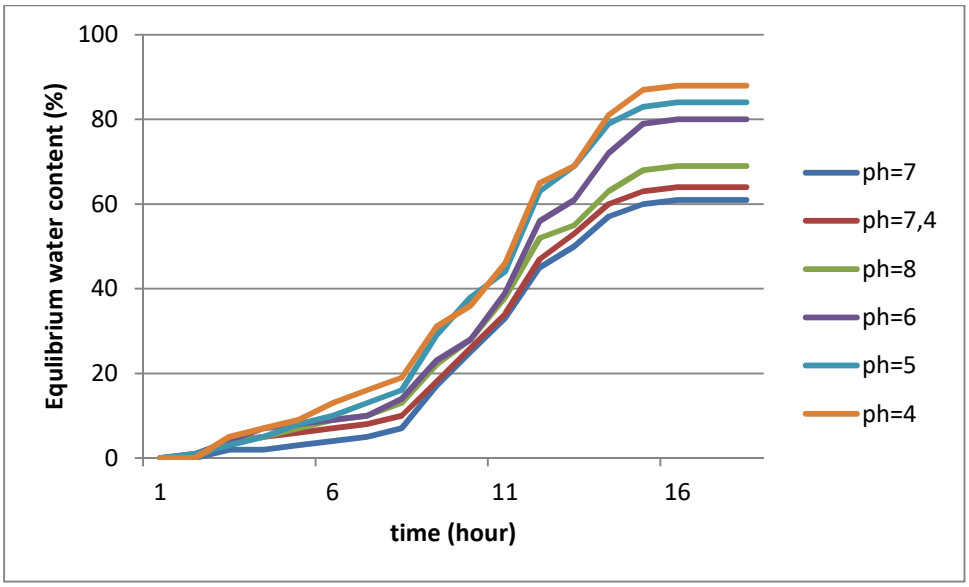

Figure 3: The swelling behavior of pHEMA-MMA hydrogel in different buffer systems.

Controlled release of the drugs varies depending on the structure of the polymer and glass transition temperature (T_g) value, which is a parameter indicating polymeric flexibility. Figure 4 shows the data obtained from DSC analyses performed under nitrogen gas at 10 °C/min heating ratio.

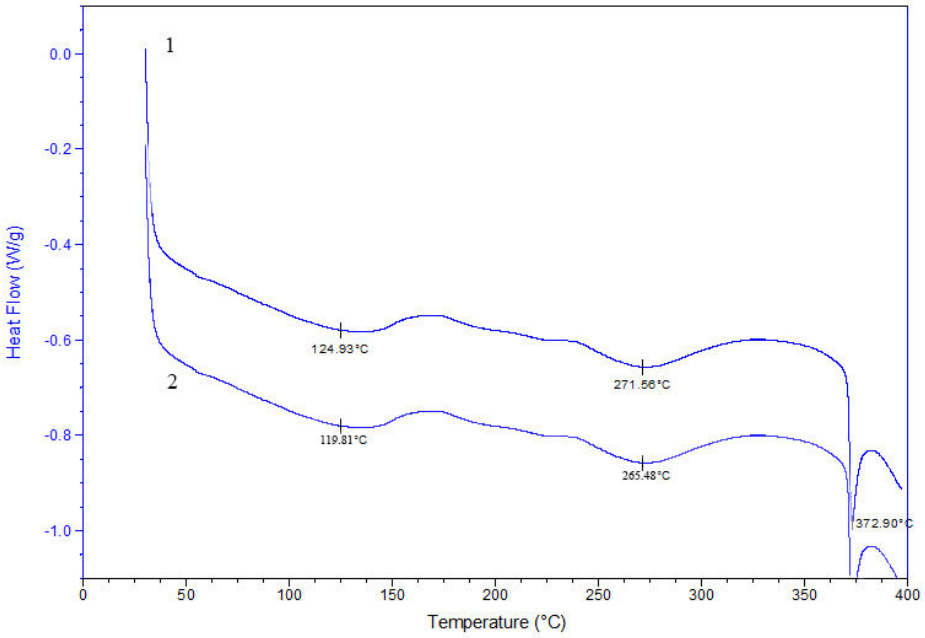

Figure 4: DSC chart of p[HEMA-MMA] [1] and pHEMA [2] hydrogels.

Contact angle values measured after dropping different test fluids (water, glycerol, diiodomethane) on pHEMA and p(HEMA-MMA) polymeric structures were determined by static drop method. (Table 2). Based on Young's equation, contact angles measured using the test fluids, which have lower surface tensions, should be smaller. Free surface

energy parameters of the polymeric structures were calculated using the contact angle values of the analyzed fluids. Total free surface energies (γ^{Total}) were calculated by van Oss' method. Table 3 shows the free surface energy parameters of the membranes based on van Oss' method.

Table 2: Surface contact angles [γerg: the surface tension of test liquid] measured with test fluids for the carrier implant.

Implant	Water [n=71.3] [Θ^0]	Glycerol [n=64.0][Θ^0]	Diiodomethane [n=50.8] [Θ^0]
PHEMA	59.2	55.5	34.3
p[HEMA-MMA]	52.4	60.0	31.1

[n: The test liquid and the surface tensions].

Table 3: Parameters of the surface free energy of the membranes [mJ/m^2] according to van Oss.

	γ^{LW}	γ^+	γ^-	γ^{AB}	γTotal	Polarity [%]
PHEMA	38.7	0.7	3.1	2.8	31.5	6.8
p[HEMA-MMA]	33.0	0.5	3.4	4.8	39.4	10.1

γ^{LW}[mN/m^2] Showing long-range interactions [dispersive interactions include dipole-dipole interaction and dipole-induced dipole interaction]

γ^+[mN/m^2] : It shows the acid component of the membrane.

γ^-[mN/m^2] : It shows some components of the membrane.

γ^{AB}[mN/m^2] : symptoms of acid-base interactions

γ^{Total}[mN/m^2] : The total surface free energy

Polarity F [%]: % polarity

Albumin adsorption to pHEMA and/or p(HEMA-MMA) carrier implant systems synthesized to be used for controlled digoxin release is important to increase biocompatibility of the prepared biomaterial. Moreover, fibrinogen adsorption to biomaterial surface reduces the biocompatibility of the prepared biomaterial. While albumin prevents thrombocytes binding to biomaterial surface, fibrinogen acts to initiate binding of thrombocytes to biomaterial surface. Therefore, albumin and PEG were placed into the prepared biomaterial by intra-matrix entrapment method, with an aim to increase blood-compatibility of the biomaterial. Serum protein levels adsorbed by pHEMA and p(HEMA-MMA) structures are shown in Table 4.

Table 4: The amounts of serum proteins adsorbed to the structure of pHEMA and P[HEMA-MMA].

	Plasma Proteins		
	HSA [ng/cm²]	**ɣ-globulins** [ng/cm²]	**Fibrinogen** [ng/cm²]
PHEMA	359	199	98
p[HEMA-MMA]	188	131	34

Release of digoxin loaded to p(HEMA-MMA) hydrogel was determined by analyses of the samples obtained from the controlled release system at regular time points over a period of 25 days. Cumulative release profile over time of p(HEMA-MMA) carrier implants was estimated. (Figure-5).

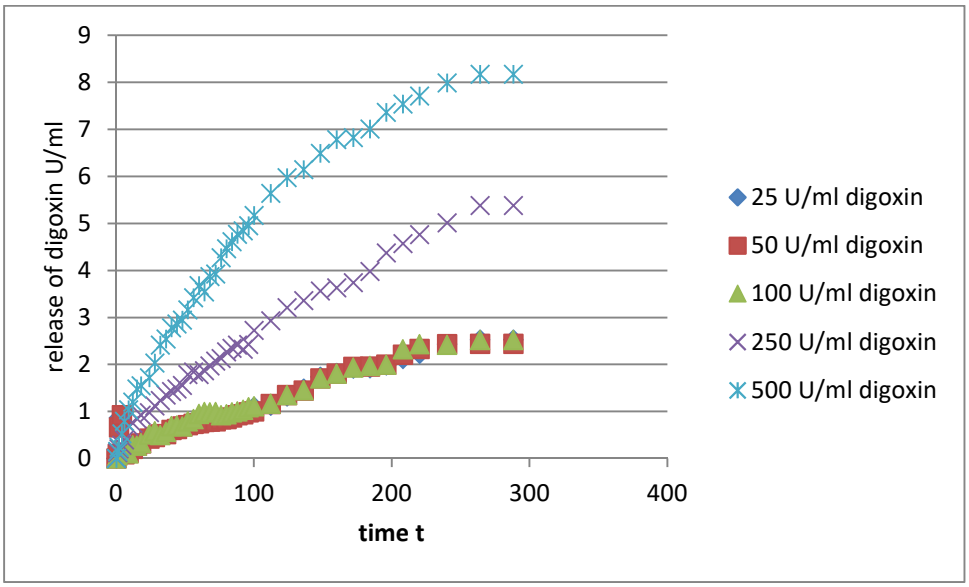

Figure 5: The oscillation profile of Digoxin from p[HEMA-MMA] hydrogel.

Figure-6 shows cumulative percent release profile over time of p(HEMA-MMA) hydrogels. The mechanism of the kinetics of controlled digoxin release from the biocompatible carrier implant was assessed using the semi-logarithmic method suggested by Korsmeyer-Peppas [9]. Experimental data obtained from controlled digoxin release system were adapted to that model in order to estimate n value. Table 5 shows the values obtained for pHEMA and p(HEMA-MMA) hydrogel with a cylindrical geometry. Values obtained for n and k release parameters in this study were consistent. Values estimated for n parameters of the biocompatible pHEMA ve p(HEMA-MMA) hydrogels prepared for controlled digoxin release were between 0.6-0.68 0.53-0.75 respectively, indicating that the kinetics of the release system represents a non-Fick transportation mechanism and the velocity of digoxin release depends on time. Another release

parameter, k, is a constant reflecting the structure and geometric characteristics of the carrier implant. Lower k values indicate slower digoxin release.

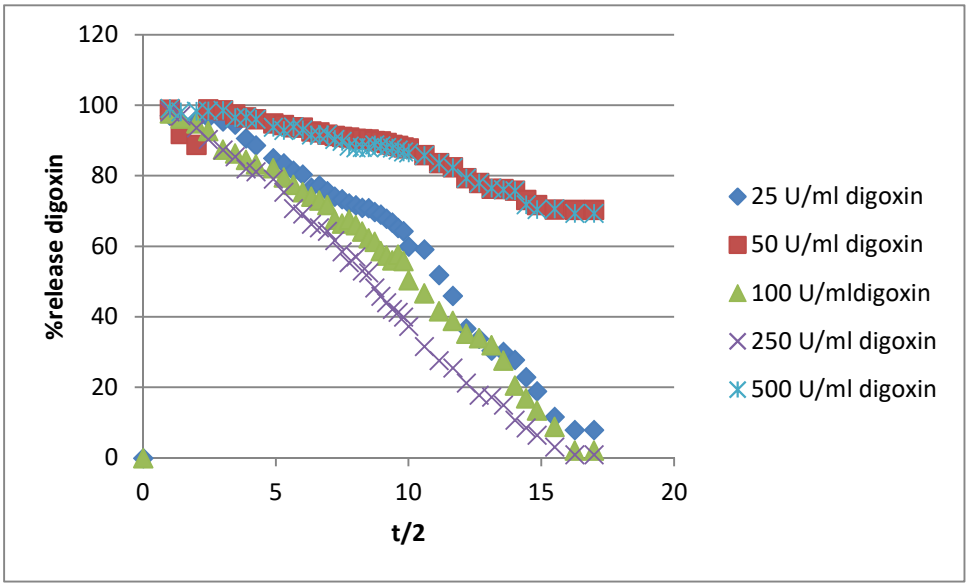

Figure 6: % cumulative oscillation chart of Digoxin from p[HEMA-MMA] hydrogel versus time (t = hours).

DISCUSSION

Controlled release parameters that should be taken into consideration while designing carrier implant systems include the characteristics of the active ingredient, the mode of administration of the drug, target region, duration of treatment, status of the disease, and the patient. Studies are performed with an idea to develop a controlled release system by loading digoxin into polymeric carrier implants, which can then be placed into cancerous tissues by surgical methods.

In the present study, pHEMA-based composite membranes in hydrogel structure, intended to bear the above listed characteristics, were synthesized using UV photopolymerization method. We believe that this newly synthesized composite membrane offers advantages to use for controlled drug release as;

i) it has sufficient mechanical power and is resistant to biological and chemical decay,

ii) it allows preparation of the required surface structure, at the required level of porosity,

iii) the drug can be loaded without causing any loss or decrease in drug activity while preparing the composite material and the carrier system allows adjusting the medication dose to any level,

iv) it has a hydrophilic structure.

Hydrogel images obtained using scanning electron microscopy indicate that the HEMA monomer, used as a component of the composite membrane, provides the material with

sufficient mechanical strength, while the pore size can also be adjusted by changing the concentration of pore-adjusting agents added to the polymerization mixture. This characteristic allows considerably fast and controlled drug release.

Inflation behavior of the hydrogels which can be inflated by solvent transfer was investigated and it was found to reduce polymer/co-polymer and co-polymer/drug interactions. pHEMA and p(HEMA-MMA) transited to aqueous structure and reached a balance in 21 and 12 hours, respectively. Water content at balanced state of p(HEMA-MMA) copolymer hydrogel in physiological phosphate buffer was found to be lower compared to pHEMA .

Presence of polar groups in the polymer increases Tg value as it reduces the motion around the main chain. Tg value of the polymer can be measured by DSC and DTA analyses. Thermal stability showed a reduction by the addition of MMA comonomer into the structure of pHEMA hydrogel.

Results of contact angle measurements showed that the surface energies of the membrane samples calculated based on Fowkes and Wu methods were comparable, but compared to the Fowkes' method, the Wu method indicated a lower polar component of the surface energy (γ^p). Both methods showed that the dispersive components made the major contribution to total free surface energy for all tested membranes. van Oss' method reflects the sum of Lifshitz-van der Waals (γ^{LW}) and acid-base components (γ^{AB}) applied at different values to all tested membranes. Base components (γ^-) of the membranes were found to be higher as compared to their acidic components (γ^+).

Presence of albumin and PEG in pHEMA and p(HEMA-MMA) structure lead to negligible levels of blood serum proteins adsorbed by the surface of the carrier implants.

Different release kinetic models were applied to experimental data to clarify the mechanism of digoxin release and the best model that defines kinetic model of release was investigated. The mechanism of the kinetics of controlled digoxin release from the biocompatible carrier implant was assessed using the semi-logarithmic model suggested by Korsmeyer-Peppas [13]. In release systems where the carrier implants used for controlled drug release have a cylindric geometry, the release mechanisms are determined by the values of the n parameter. Based on this model, an n parameter of 0.45 is defined by Fick's diffusion mechanism, while values between 0.45 - 0.89 reflect non-Fick mechanism, a value equal to 0.89 shows State II (relaxations) transportation and values higher than 0.89 indicate super State II tranportation mechanisms [13-15].

Another release parameter, k, is a constant reflecting the structure and geometric characteristics of the carrier implant. Lower k values indicate slower digoxin release. In the present study, estimated n and k release parameters were consistent. Values of the n parameters, calculated to be between 0.6-0.68 and 0.53-0.75, respectively, for the biocompatible pHEMA and p(HEMA-MMA) hydrogels prepared to be used for controlled digoxin release, indicated that the kinetics of the release system can be defined by a non-Fick transportation mechanism and the velocity of digoxin release depends on time. The compatibility of digoxin-release profile from the biocompatible p(HEMA-MMA) hydrogels with zero-degree kinetics and the Higuchi model was investigated, and analyses of the estimated model parameters showed that the results were consistent with both models.

Release-periods investigated after loading digoxin into p(HEMA-MMA) hydrogel demonstrated that the release process continued over a long period, as intended.

In conclusion, the present study showed that the developed formulation can be successfully used to provide basal digoxin levels for more than 3 weeks. These findings indicate that the hydrogel-based biocompatible implant materials prepared for this study provide several different advantages such as easy sterilization and drug loading, adjustment of the sample dose, biocompatibility of the system and elimination of the need to use organic solvents.

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Türkçe Öz ve Anahtar Kelimeler

Kontrollü Digoksin Alımında Kullanılmak Üzere Biyo-uyumlu Taşıyıcı İmplantın Hazırlanması ve Uygulanması

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Öz: Bu çalışmada, kalp yemezliğinin tedavisinde yavaş bazal digoksin salınımına katkıda bulunan sabit bir sistem ortaya konmuştur. Poli(2-hidroksietil metakrilat – metilmetakrilat) (p(HEMA-MMA)) kopolimeri UV fotopolimerizasyonu ile silindirik yapıda hazırlanır ve su tutarak şişer. Poli(HEMA-MMA) bileşimine sahip bir örnek farklı monomer oranlarında hazırlanmıştır. Biyo-uyumluluk PEO, PEG ve serum albuminat yapılarının p(HEMA-MMA)'ya ilave edilmesi ile geliştirilmiştir. Taramalı elektron mikroskobu (SEM) çalışmaları hazırlanan taşıyıcı implant malzemesinin yüzey yapısını çalışmak için kullanılmıştır. Diferansiyel taramalı kalorimetri (DSC) çalışmaları da ısıl kararlılık analizlerinde kullanılmıştır. Şişme davranışları, çözücü moleküllerini hidrojellere aktararak incelenmiştir. Digoksin salım kinetiği üç farklı akümülatif digoksin dozunun (100, 250 ve 500 U/mL) fizyolojik fosfat içeren sabit akış salım sistemine verilmesiyle değerlendirilmiştir. Güç yasası, sıfır seviyesi ve Higuchi model eşitlikleri uygulanarak digoksinin salım mekanizması değerlendirilmiştir En uygun sonuçlar, HEMA:MMA monomer oranının 1:0,5 (v/v) olduğu durum için ilaç birikmesi ve salım çalışmalarında elde edilmiştir. SEM görüntülerinden görüldüğü kadarı ile, alınan hidrojelin yapısı içinde taşıyıcı implant yumuşak bir yüzeye sahiptir. DSC sonuçlarına göre, ısıl kararlılığın MMA komonomerinin pHEMA hidrojeline eklendiği durumlarda azaldığı görülmüştür. Poli(HEMA-MMA) kopolimerinin fizyolojik fosfat tamponu içindeki denge suyu miktarı pHEMA'dan daha az olarak bulunmuştur. Taşıyıcı implantlara yüklenen digoksin salımı farklı oranlar kullanıldığında beklendiği gibi uzun dönem zaman almaktadır. Kronik kalp yetmezliğinin tedavisinde, çalışmada önerilen formülasyon temel digoksin seviyesinin dört haftadan daha uzun süre başarıyla uygulanabilmesini sağlamaktadır.

Anahtar kelimeler: pHEMA; p[HEMA-MMA]; taşıyıcı implant; digoksin; kontrollü salım.**Sunulma:** 21 Eylül 2016. **Düzeltme:** 30 Eylül 2016. **Kabul:** 20 Aralık 2016.