MODELLING OF DRUG RELEASE KINETICS FROM SPHERICAL PEGDA HYDROGELS

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Abstract

Hydrogels are attractive controlled delivery systems of drugs due to higher surface to volume ratio compared to macroscopic systems. In the scope of the presented work, PEG-DA based spherical hydrogels were synthesized, characterized, and. in vitro controlled release kinetics of the drug from microspheres for different PEG-DA and photoinitiator ratios were investigated with various mathematical models.

In the first part of the work, synthesis of PEG-DA based spherical hydrogels by free-radical photopolymerization method by using photoinitiator was done. Polyethylene glycol diacrylate (PEG-DA) was used as macromer, ethylene glycol dimetacrylate (EGDMA) and 2,2 dimetoxy-2 phenylacetophenon (DMPA) were used as cross-linking agent and photoinitiator, respectively. In order to observe the effects of the amounts of the compounds, the ratios of the macromers was tested at 30 and 50 % by weight and photoinitiator ratio was arranged as 0.5 and 1 % by weight while cross-linker ratio was kept constant as 1 % by weight. The chemical characterizations of hydrogel were performed with ATR-FTIR (Attenuated Total Reflectance-Fourier Transform Infrared Spectroscopy) spectrums of hydrogels synthesized in the disc form with the same compositions and the characteristic pikes of PEG-DA was observed. Optic microscope images of synthesized, microspheres were taken.

Then drug release experiments of polymer spherical hydrogels with known weight and gentamicin amount, were performed in pH 7 and pH 2 buffer solutions with certain ionic strengths. The drug release kinetic models, zero order, first order, second order, Hixson-Crowell, Weibull, Higuchi, Baker-Lonsdale, and Korsmeyer-Peppas mathematical models were selected. The data were arranged for each hydrogel group according to mathematical models from the graphical change of drug delivery results obtained with time. The mathematical models with highest regression coefficients, in other words the most suitable models for in vitro controlled drug release from PEGDA microspheres were predicted using MATLAB program.

Keywords: *Poly(ethylene glycol) diacrylate, Photopolymerization, Spherical hydrogels, Controlled drug release, Mathematical modeling*

1. INTRODUCTION

Micro and nanoparticles occupy in an important position in drug delivery technology due to tendency to accumulate in various areas of the body. The polymeric systems, either synthetic or natural are used to develop Controlled Release formulations to achieve the maximum concentration of drug to the target site minimizing side effects. Hydrogel microspheres are composed of three dimensional polymer chain networks that are cross-linked either by covalent or physical bonds. PEG hydrogels formed through the photopolymerization of poly(ethylene glycol) diacrylate (PEG-DA) and used these gels for the prevention of restenosis, post-surgical wound adhesions, the release of various drug compounds such as proxyphylline, caffeine, and etc.

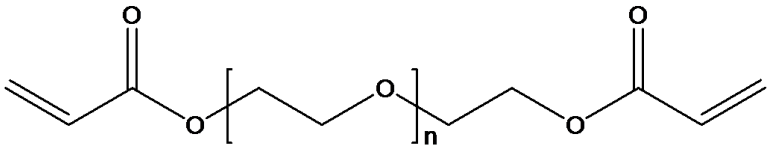


Fig. 1. The structure of PEG-DA

The reason for the choice of free radical polymerization method for the synthesis of hydrogels, polymerization takes place very quickly no organic solvent is needed and, PEG-DA macromer was preferred because of its high biocompatibility, no harmful effect, flexibility, ability to control cross-linking density and water uptake, etc.

Mathematical modeling of drug delivery and predictability of drug release is a field of steadily increasing academic and industrial importance with an enormous future potential. The control of drug release offers: the quantitative analysis of the physical, chemical and potentially biological phenomena and elucidation of the underlying drug release mechanisms as another fundamental advantage. Model dependent methods are Zero order, First order, Higuchi, Korsmeyer-Peppas model, Hixson Crowell, Baker-Lonsdale model, Weibull model, etc. This work contains the synthesis of PEG-DA based spherical hydrogels, characterization of spherical hydrogels experiments of drug release, kinetic models for releasing, and solution of models.

2. MATERIALS AND METHODS

2.1. Materials

Poly(ethylene glycol)-diacrylate (PEG-DA, Mn: 575), 2-hydroxyethyl methacrylate (HEMA), cross-linking agent ethylene glycol dimethacrylate (EGDMA), and 2,2-dimethoxy-2-phenyl-acetophenone (DMPA) were obtained from Aldrich Chemical Company. All materials were used as received and all other chemicals were of reagent grade.

2.2. Methods

Macromers 30 wt % and 50 wt % PEG-DA (Mn:575) and 0.5 wt % DMPA (macromer based) were mixed. Gentamicin sulphate solution (Genta,İ.E. Ulagay İlaç Sanayi) of certain gentamicin amount (18 mg/g polymer) and cross linking agent, ethylene glycol dimethacrylate (EGDMA) was added at a concentration of 1 wt % based on macromer weight up to the final volume. Final solution was purged with nitrogen for a few minutes. Polymer hydrogel spheres were formed by dispensing 0.5 and 2 µl of the precursor solution in mineral oil by using a micropipette. Photopolymerization was performed by a 365 nm, 20 mW/cm2 UV lamp light intensity, which illuminated the spherical droplets of precursor solution in the mineral oil. Precursor solution residence time in the UV light path was approximately 3-5 second. The polymerized spheres were collected, rinsed with *n*-hexane or *n*-heptane. The chemical characterizations of hydrogel were performed with ATR-FTIR (Attenuated Total Reflectance-Fourier Transform Infrared Spectroscopy) spectrums. Optic microscopy images of spherical PEGDA hydrogels were taken Gentamicin release of hydrogel microspheres. Hydrogel microspheres was placed in a vial containing 10 ml buffer solution at 37◦C with constant stirring. Release kinetics were tested spectrophotometricaly at 255 nm in phosphate buffer (pH 7.4) and citrate buffer (pH 2) with the ionic strengths of 0.13 M by the addition of KCl. At predetermined time points, the amount of gentamicin sulphate and cumulative fractional release at time t of the 18 mg/g polymer loaded sample was then calculated.

The drug release kinetic models, Zero order, First order, Second order, **H**ixson-Crowell, Weibull, Higuchi, Baker-Lonsdale, and Korsmeyer-Peppas were selected. MATLAB program were used to predict the mathematical models with highest regression coefficients, in other words the most suitable models for *in vitro* controlled drug release from PEGDA microspheres.

3. RESULTS

ATR-FTIR results conforms the realization of photopolymerization by the dissaprearance of Stretch vibration bands for pure PEG-DA (O-H: 3000-3700 cm^{-1}, C-H: 2700-3300 cm^{-1}, C=O 1600-1900 cm^{-1}, C-O: 900-1300 cm^{-1}). Optical microscopy images shows that spherical PEG-DA hydrogel diameters are 635,72±50 µm, and 1020,51±80 µm.

Drug release rates were estimated and cumulative release rates were determined. The experimental results were used to calculate the regression coefficients of the proposed models at different pH, photoinitiator for 30 and 50 % macromer content values. The average regression coefficient values were calculated for each macromer ratios at pH 7.4 and 2. The application of Higuchi model resulted with regression coefficients between 0.9146-0.9026 for both sphere diameters and release pH values. The highest regression coefficients were estimated for Korsmeyer-Peppas mathematical model especially for drug release at pH 7.4 of 50 % macromer ratio and at pH 2 for 30 % PEG-DA ratio.

4. DISCUSSION

Mathematical modelling of model drug gentamicin release from PEG-DA hydrogels showed the importance of model selection in kinetic modelling. The models with the highest regression coefficient greatly comply with the shape of hydrogel. So, spherical micro hydrogels showed drug release behaviours which can be analysed with Weibull, Korsmeyer-Peppas and Higuchi mathematical models for in vitro biomedical applications.

5. CONCLUSIONS

PEG-DA based spherical hydrogels; were synthesized; were characterized; the mathematical models in vitro controlled drug release from microsphere hydrogels with different PEG-DA and photoinitiator ratios. The mathematical models with highest regression coefficients, in other words the most suitable models used in in vitro controlled drug release were predicted as Weibull, Korsmeyer-Peppas, and Hifuchi models with the highest regression coefficient for both spherical hydrogels with different diameters. The investigated models can be used primarily in the modelling drug release kinetics from spherical hydrogels.

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