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Stimuli-responsive molecularly imprinted hybrid polymer gel as a potential system for controlled release

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ABSTRACT: The purpose of this study is to develop a stimuli-responsive hybrid polymer gel system with an improved mechanical stability as a controlled drug delivery carrier that can undergo phase transition by the stimulation of ethanol–water mixture. For this aim, trimethoxysilane terminated poly(propylene glycol) by coupling of 3-isocyanatopropyl-triethoxysilane with the hydroxyl end groups of poly(propylene glycol) through urethane bonds was synthesized. Hybrid polymer gels prepared in the presence of tryptophan (Trp), as a model of drug, were characterized and gelation time of polymer network was obtained by monitoring the fluorescence emission of Trp in pre-gel solution. Swelling, solvent uptake and release kinetic of polymer gels were evaluated depending on time. The diffusional exponents (n) and diffusion constants (k) of each gel were calculated by using the swelling kinetic data. The effect of precursors as a monomer on Trp release profile was analyzed. © 2015 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2016**, *133*, 42913.

KEYWORDS: drug delivery systems; gels; molecular recognition; stimuli-sensitive polymers; swelling

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INTRODUCTION

Tryptophan (Trp) is one of the 20 essential amino acids that constitute proteins. Human body could not produce Trp but can only be consumed from diet and Trp is also vital to the production of serotonin and melatonin.[1,2] One of these two hormones serotonin helps to adjust moods, sound sleep, temper anxiety, and relieve depression. A lack of Trp contributes to coronary artery spasm and Hartnup disease.[3,4] General symptoms of Trp deficiency as basically similar to serotonin deficiency and include: anxiety and panic, mood disorders, irritability, insomnia, aggressiveness.[5] For these reasons, the development of a simple, accurate, rapid and inexpensive method for the controlled release of Trp would be valuable.

The growing interest in sol-gel science is due to the straightforwardness in tailoring the porosity in these materials, particularly in achieving molecular recognition in different systems such as adsorption or absorption, stationary phases in liquid or gas chromatography, and chemical sensing applications.[6] The production of sol-gel materials provides numerous advantages over the other conventional synthetic schemes. One of the major advantages is that these systems allow the manufacturing at low temperatures, which enables us to generate functionalized matrices, where others lack this ability.[7] Different strategies used to combine organic components with inorganic components at the molecular level have enabled the development of new advanced materials that display innovative functionalities.[8] The ability to control drug delivery using hybrid materials is attractive to professionals in the pharmaceutical, chemical, and materials science fields, since such hybrids offer numerous advantages over conventional drug carriers.[9,10] The controlled release of the drug has been mainly controlled by controlling the molecular weight of the polymeric device and the drug-loading content.[11–13] When the device is used purely as a drug delivery carrier, the polymer must not interact with the drug, and the completeness of device degradation must coincide with the end of the drug release.[14,15]

Stimuli-responsive or smart polymers are macromolecules that display a significant physiochemical change in response to small changes in their environment such as temperature, pH, light, magnetic field, ionic factors, etc.[16,17] Sol-gels have a porous network which we can control the porosity by controlling the density of cross-links or by changing the swell affinity in the environment.[18,19] This porosity property of sol-gels helps the release of drugs from the gel network. The release of drug from sol-gels can be controlled by controlling the diffusion coefficient of drugs through sol-gel matrix.[20]

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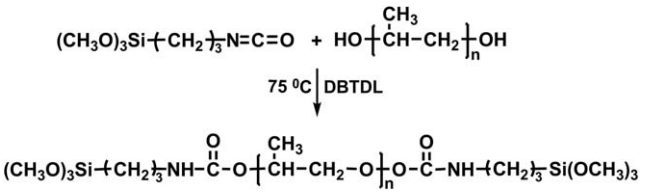

Figure 1. The synthesis scheme of PPG-ICPTS.

Molecular imprinting is a technique to synthesize highly cross-linked polymers with a predetermined selectivity and specificity for a given analyte.[21] In molecular imprinting processes, one needs a template, functional monomers, cross-linker(s), initiator, porogenic solvent.[22,23] Molecular imprinting technique has been widely and successfully used to prepare polymers offering high affinity binding sites for a variety of molecules, including organic, inorganic, and even biological molecules or ions.[24,25] Molecular imprinted polymers have been used considerably in drug delivery systems.[26–28]

In this study, trimethoxysilane terminated poly(propylene glycol) (PPG-ICPTS) was synthesized by coupling reaction of 3-isocyanatopropyltriethoxysilane (ICPTS) with the hydroxyl end groups of poly(propylene glycol) (PPG) through urethane bonds. PPG was introduced as a chain extender to improve the mechanical stability and aminopropyltriethoxysilane (APTES) was incorporated as a functional precursor. Imprinted polymer gel films were prepared by using PPG-ICPTS and functional precursor in the presence of Trp. Nonimprinted polymer gel film was obtained at the conditions similar to imprinted gel in the absence of Trp and also prepared in the presence of Trp by using precursor with low affinity toward Trp. Solvent uptake and drug release properties of hybrid gels in ethanol–water mixtures with different compositions were elucidated.

EXPERIMENTAL

Materials and Methods

Materials. Poly(propylene glycol) (PPG) with a molecular weight of 3900 g mol^{-1} and 3-isocyanatopropyltrimethoxysilane (ICPTS) were obtained from Alfa-easer company and dibutyltindilaurate (DBTL) was provided by TIB Chemical Company. Tetramethoxysilane (TMOS), methyltrimethoxysilane (MTMOS), and aminopropyltrimethoxysilane (APTES) were purchased from Aldrich. Tryptophan and dibutylamine were obtained from Fluka. Organic solvents; diethylether, tetrahydrofuran, ethanol, and the other chemicals were supplied by Merck. All these chemicals were used as received.

Equipments and Instrumentations. The information about the chemical bonding and molecular structure of hybrid gels were obtained by using Attenuated Total Reflectance-Infrared (ATR-FT-IR) spectrophotometer of Perkin–Elmer, Spectrum One with a commercial software Spectrum v5.0.1. Varian Cary Eclipse Fluorescence Spectrophotometer was used for measuring fluorescence emission of both Trp in solution and the surface of the gel samples. The change in pH was measured by pH meter, WTW inoLab pH 730.

Preparation of PPG-ICPTS. Polypropylene glycol (PPG) was dried in vacuum drier at 100°C overnight and 10 g of PPG was dissolved in dry THF. Then, dibutyltin dilaurate (DBTDL) and 3-isocyanatopropyltrimethoxysilane (ICPTS) were added drop by drop for about 1 h in nitrogen atmosphere and mixture was stirred continuously for 24 h under reflux at 75°C. Then the solvent was removed by rotary evaporation and residue was directly purified by washing with ether. PPG-ICPTS was obtained after drying in a vacuum oven (Figure 1).

Preparation of Hybrid Gels with Tryptophan. Hybrid gels with Trp were prepared by using 0.65 mL of ethanol and the amounts of components were given in Table I. Hybrid gels were prepared in the presence of Trp by using PPG-ICPTS as spacer, TMOS as cross-linker, APTES as functional precursor, MTMOS as precursor, dibutylamine (DBA) as catalyzer. The mixture then was allowed to hydrolyze and the hybrid gels were obtained in the presence of Trp. As shown in Figure 2, Film-A and Film-B are imprinted hybrid gels since they contain functional precursor, APTES which has ability to form complex with target molecule, Trp. Film-C and Film-D are nonimprinted hybrid gels since they contain precursor which has low affinity toward Trp. Meanwhile, Film-A and Film-C additionally contain tetra functional precursor, TMOS. Similar procedure with APTES and without Trp was also used to prepare nonimprinted hybrid gel.

Solvent Uptake Experiments in Ethanol–Water Mixtures. The dried hybrid sol-gels (Film-A, Film-B, Film-C, and Film-D) were weighed and put into ethanol–water mixtures with different compositions for 7 days. Then, change in mass was recorded by weighting the gels depending on time. The amounts of solvent uptake by 1 g of gels were calculated by using eq. (2.1):

$$\text{Solvent uptake} = \frac{W_t - W_d}{W_d} \quad (2.1)$$

where, W_t is the weight of gel at time t, W_d is the weight of dry gel.

Solvent Release Experiments in Distilled Water. After The hybrid sol-gels films were swollen in ethanol–water mixtures for 7 days, the gels were placed into separate polypropylene tubes and were deswelled in water at ambient temperature in different incubation times. Then, change in mass was measured

Table I. The Amounts of Chemicals used in Synthesis of Polymer Gels with Trp

Samples	PPG-ICPTS (g)	APTES (mmol)	TMOS (mmol)	MTMOS (mmol)	DBA (μL)	0.05*M* Trp (μL)
Film-A	0.35	0.2	0.2	–	–	35
Film-B	0.35	0.2	–	–	–	35
Film-C	0.35	–	0.2	0.2	35	35
Film-D	0.35	–	–	0.2	35	35

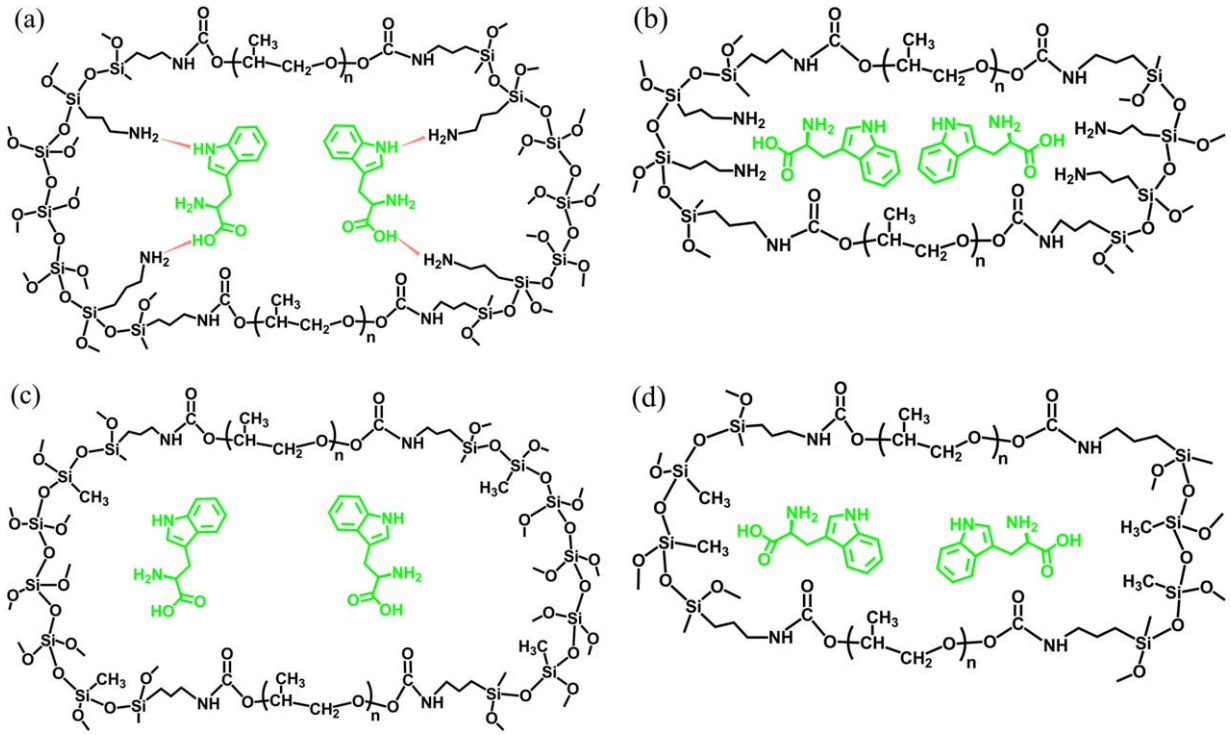

Figure 2. Molecular structures of polymer gels with Trp. a) Film-A, b) Film-B, c) Film-C, d) Film-D. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

depending on time. Furthermore, the concentrations of Trp released by films were monitored by fluorescence spectroscopy with respect to time. The solvent retention and the amounts of solvent release by 1 g of gels (g-solvent/g-gel) were calculated by the eq. (2.2)

$$\text{Solvent retention} = \frac{W_r - W_d}{W_s} \qquad (2.2)$$

where, W_r is the weight of deswelled gel at time t, W_d is the weight of dry gel, and W_s is the weight of gel at swelling equilibrium.

Evaluation of Trp Released by Hybrid Gels. Hybrid gel films were placed into the mixture and then fluorescence emission spectra of the solutions were recorded depending on time. Concentration of Trp was calculated using each calibration curve obtained in different solvent mixtures. Trp released by 1 g of gels were calculated using dried weights of gels. The views of hybrid polymer gels were given before and after applying the processes (Supporting Information Figure S1).

RESULTS AND DISCUSSION

FT-IR Characterization of PPG-ICPTS and Hybrid Gels

The purified hydrophilic silicon-containing functional groups were identified using Attenuated Total Reflectance-Infrared (ATR-FT-IR). In addition, a comparison of the IR spectra before and after the reaction reveals that a peak representing the cyanate group (–N=C=O), which contributes a strong vibration band at 2260 cm^{-1}, is clearly seen in the ICPTS spectrum and completely disappears in the PPG-ICPTS spectrum (Figure 3). Moreover, a peak representing carbonyl (–C=O) was generated at 1715 cm^{-1} and the band of hydroxyl (-OH) from PPG at 3485 cm^{-1} disappeared in IR spectrum after the coupling reaction since hydroxyl groups at the terminal end of PPG reacted to form amide bond [–NH–(C=O)].

ATR-FT-IR spectra of hybrid gels were obtained and showed the presence of typical silica bands relative to the inorganic framework (Figure 4). The vibration band of the siloxane (Si-O-Si) group is shown at about the broad band around 1088 cm^{-1}.[29] The bending frequency of the Si–OH band is seen at about 925 cm^{-1}. Peak at, 1342 cm^{-1} is due to the vibrations of

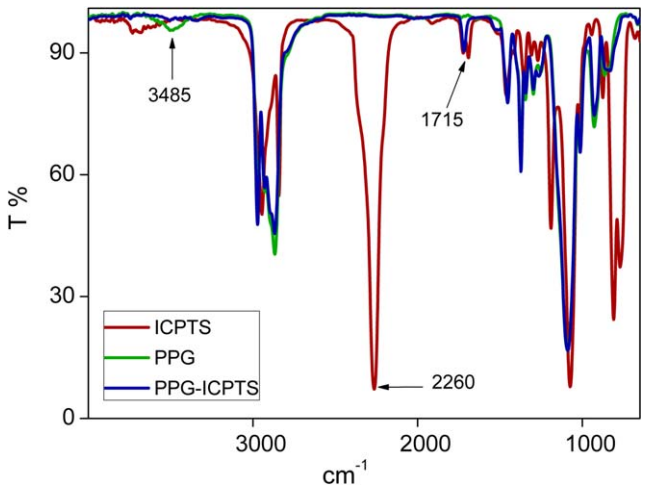

Figure 3. FT-IR spectra of ICPTS, PPG and PPG-ICPTS. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

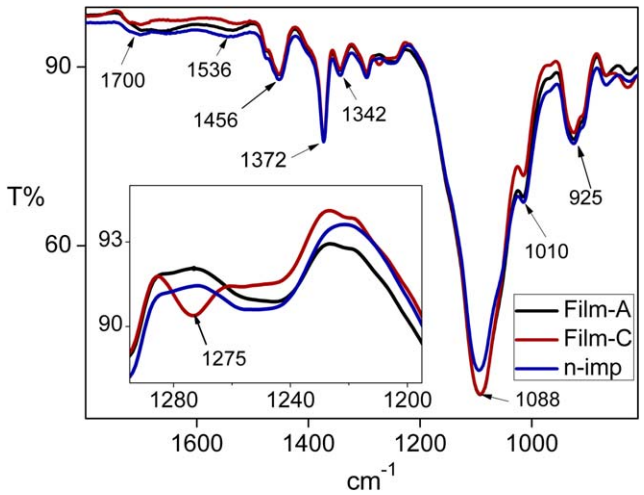

Figure 4. FT-IR spectra of Film-A, Film-C, and N-imp polymer gels. Inset: An enlargement of the spectra showing the bands between 1175 and 1300 cm^{-1}. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

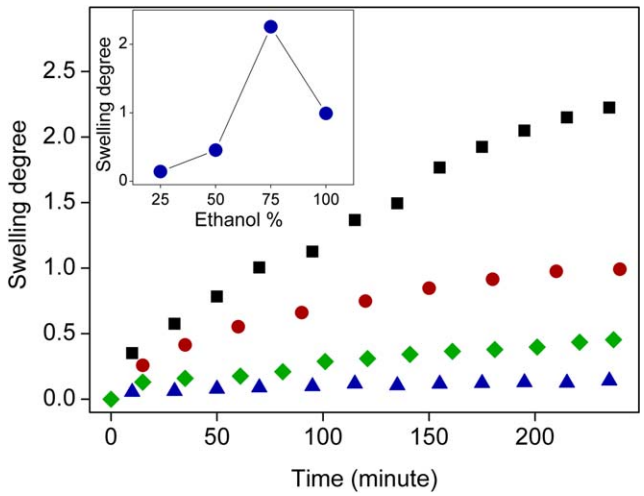

Figure 6. Swelling degree of non-imprinted hybrid gel depending on solvent composition. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

methylene groups in the APTES precursor. Therefore, the absorption bands at 1342 cm^{-1} and 1372 cm^{-1} can be assigned to the Si-CH_2 stretching.[30] The remaining spectral features include an absorbance feature at 1536 cm^{-1}, corresponding to NH_2 scissor vibration and confirming the presence of the NH_2 terminal group of APTES molecules.[31] The band at 1275 cm^{-1} of the MTMOS precursor in Film-C, which can be seen in the enlargement of inset of Figure 4, is due to (H-C-H) in the Si-CH_3 group.[32]

Fluorescence Spectra of Trp during Gelation

Pre-gel solution was placed into compartment of fluorescence device and emission spectra of Trp existing in pregel solution were monitored depending on time (Figure 5). As seen from Figure 5, fluorescence emission intensity of Trp increased upon reaction time, and reached to maximum. The reason for the increase in emission intensity is due to the immobilization of Trp molecule in the network of gel structure and reducing in relaxation time of Trp molecule. The network formation of hybrid gel was almost completed within the 40 min (inset Figure 5).

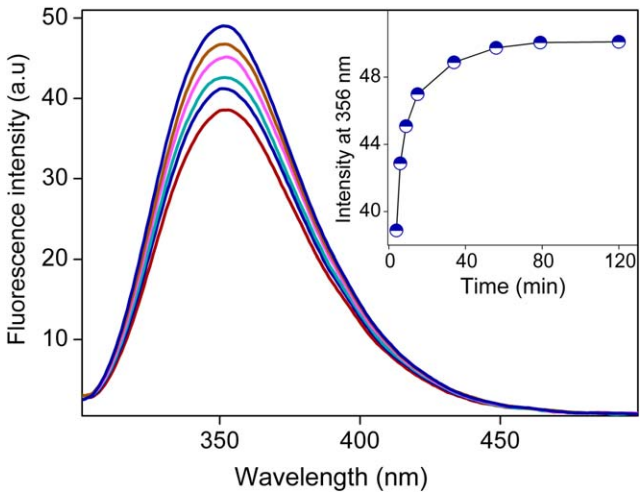

Figure 5. Change in fluorescence spectra of Trp during the polymer gel formation. Inset: emission intensity at 356 nm depending on time. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Swelling and Solvent Uptake of Hybrid Gels

The equilibrium swelling ratio of hybrid gels, which signifies the expanding and retracting forces between the crosslink at equilibrium, was determined by measurements in water and ethanol–water mixtures. The weight of the swollen sample was measured after blotting excessive solution mixture gently with filter paper. Swelling behavior of the hybrid gel in ethanol–water mixtures of different compositions was shown in Figure 6. As seen from Figure 6, when incubation time increased, the equilibrium swelling degree or solvent uptake of gel film in different solvent compositions (ethanol–water (v/v)) at ambient temperature increased. The degree of swelling in feed composition containing 75% water was found to be very low, but the value increased steadily with increasing concentration of ethanol. The swelling gradually reached to equilibrium after 270 min in ethanol–water combinations at room temperature. The highest swelling degree was observed for 75% ethanol and 25% water mixture.

The comparison between the time-dependent swelling uptakes of the hybrid gels was illustrated in Figure 7. As seen from Figure 7, Film-D adsorbed much more solvent than those of the other gels. Because Film-D contains MTMOS as a precursor having a methyl group which makes the hybrid gel more hydrophobic. The low solvent uptake of Film-C was observed when compared with Film-D. This is due to the existence of TMOS which acts as a cross-linker, causing denser network.[33] On the other hand, solvent uptake of both Film-A and Film-B were lower than those of the Film-C and Film-D. The reason for low solvent uptake of Film-A and Film-B is due to the existence of APTES that forms hydrogen bonds in network structure causing to inhibition of solvent absorption by hybrid gel. The degree of

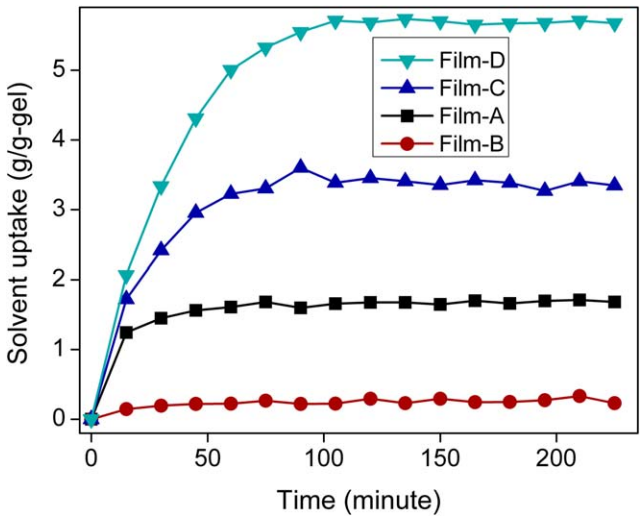

Figure 7. Solvent uptake of hybrid polymer gels in 75% ethanol and 25% water solutions depending on time. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

swelling depends on the concentration of cross-linking, function of precursor and the degree of the interest of polymer to solvent. When a hybrid gel contacts with solvent mixture, the mixture diffuses into the gel and the gel expands, resulting in swelling of the gel. Diffusion involves migration of solvent into pre-existing or dynamically formed species between gel chains. The eq. (3.1) was used to investigate the nature of diffusion mechanism, the sorption data of the solvent-gel system have been fitted to the equation.[34]

$$\log\left(\frac{M_t}{M_\infty}\right)=\log k+n\log t \tag{3.1}$$

where, M_t and M_∞ are the mass uptake of solvent or water-solvent mixtures at time t and equilibrium, respectively; k is a constant that depends on the gel morphology and the gel interaction parameter; the value of n determines the mode of transport of the solvent through the gel film. The study of diffusion

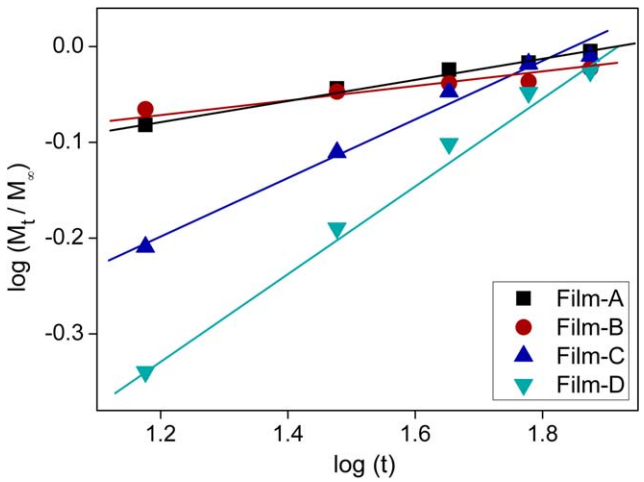

Figure 8. Plots of log (M_t/M_∞) versus log (t) for polymer gels in 75% ethanol and 25% water mixture. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table II. Diffusional Exponents (n) and Rate Constants (k) Values of each Film in Swelling Kinetic

Sample	n	k
Film-A	0.1086	0.62
Film-B	0.0555	0.74
Film-C	0.2974	0.28
Film-D	0.4612	0.13

phenomena of solvent in the gel is used to clarify gel behavior. The values of n and k were calculated from the slope and the intercept of the plot of log (M_t/M_∞) against log (t), respectively (Figure 8). The diffusional exponents (n) and calculated diffusion constants (k) are listed in Table II. As seen from Table II, the diffusional exponents and rate constants values of each film in swelling kinetic indicated the existence of pseudo-Fickian diffusion ($n < 0.5$) with different swelling rates and the orders of rate constants were inverse to the diffusional exponents.[35]

Measurement of Trp Release by Fluorescence Emission

To follow Trp release from hybrid sol-gel films in ethanol–water mixture (75–25, v/v), fluorescence spectra of solutions were monitored and recorded depending on time in the presence of each films. Calculations of Trp amount released by each film were carried out by using Trp calibration curve which was obtained in same solvent mixture (Supporting Information Figure S2). The amount of Trp release profiles a function of time for four hybrid gels which were incubated in ethanol–water mixture is shown in Figure 9. The data were collected from the gels aged in time which is necessary to reach equilibrium of swelling. As seen from Figure 9, fractional release of Trp at time interval is in the order of Film-B < Film-A < Film-D < Film-C, and Film-C showed the highest amount of Trp release at swelling equilibrium.

Meanwhile, fluorescence spectra of Trp existed on the matrix of different hybrid gel films in dry state were obtained before the

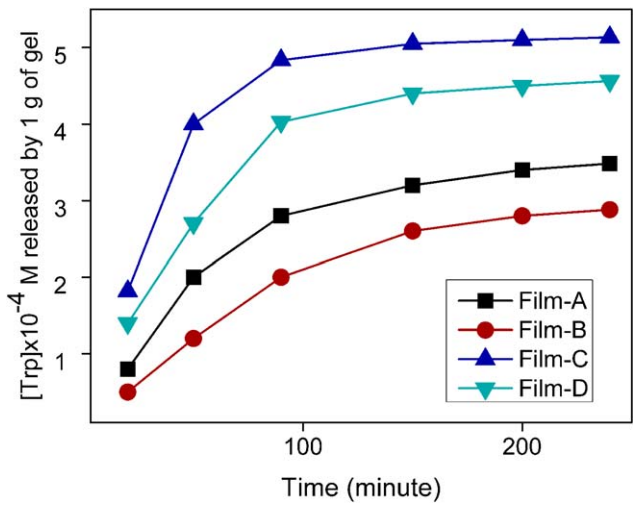

Figure 9. Fractional release of Trp from polymer gels in mixture of ethanol–water (75–25, v/v) depending on time. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

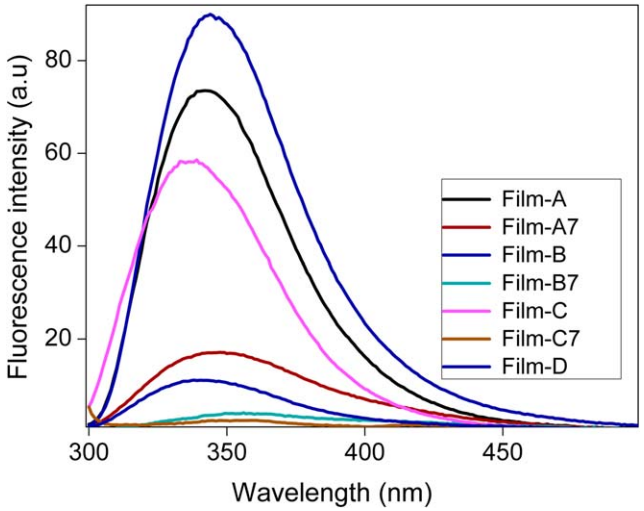

Figure 10. Fluorescence spectra of polymer gels in dry state (Film-A, B, C, D) and after 7 days immersed in 75% ethanol–25% water solutions (Film-A7, B7, C7). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

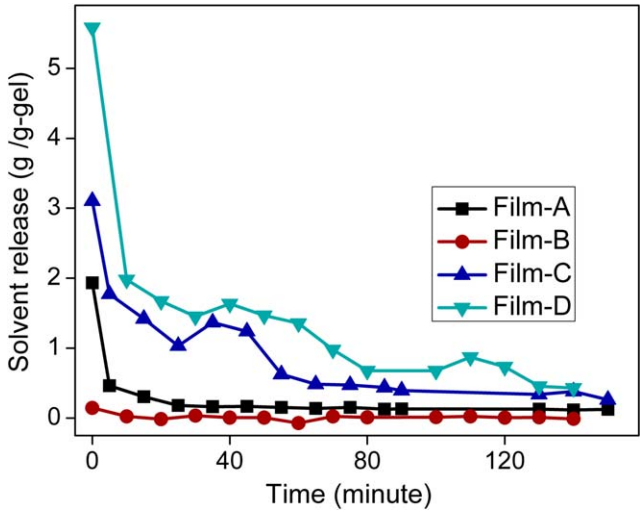

Figure 11. Solvent release from polymer gels in water depending on time. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

swelling study (Figure 10). As seen from Figure 10, Trp in Film-A, Film-B, Film-C, and Film-D exhibited maximum intensities at 342 nm, 344 nm, 335 nm, and 337 nm, respectively. After gels were incubated in ethanol–water mixture for 7 days, they were taken out from the solution and fluorescence spectra of trapped Trp in polymer gel films were measured in solvent mixture (Figure 10). It was observed that Trp in Film-A, Film-B, Film-C exhibited emission intensities at 348 nm, 345 nm, and 356 nm, respectively. The reason for shifting of emission maximum of Trp to red region is due to existence of more hydrophilic environment. The fluorescence spectrum of Film-D which was incubated for a week could not be obtained since the gel was not fitted to the quartz tube due to the having big size. As seen from Figure 10, the intensities of Trp spectra diminished upon swelling in solution, showing the release of Trp from films.

Deswelling of Hybrid Gels in Water

After all hybrid gels were swollen in ethanol–water mixture, they were immersed into a water solution for deswelling procedure and weighted depending on time. It was observed that the rate of liberation of ethanol from the hybrid gels in aqueous solution was inversely proportional to the swelling degree of gels (Figure 11). This indicates that the smaller the swelling ratio the greater the rate of liberation. During the deswelling procedure, fluorescence spectra of solutions were measured depending on time and the concentration of Trp was calculated using calibration curve obtained in water solution (Figure 12). As seen from Figure 12, hybrid sol-gel Film-C and Film-A exhibited higher Trp release compared with other films.

Solvent Uptake and Trp Release of Hybrid Gels at Low pH

Solvent uptake behavior of hybrid sol-gels at acidic conditions, pH = 1.0 revealed that absorbed amount of solvent by Film-C was higher than that of Film-A (Supporting Information Figure S3). At the same time, Film-C also absorbed much more ethanol–water (75:25) mixture at pH of 6.64 (Figure 7). When two conditions are compared it was concluded that the solvent uptake was found to increase with decreasing of pH. Cumulative release profiles of films were determined using the mathematical model or power law eq. (3.1) and calculated from the slopes of the linear portion of the curves (Supporting Information Figure S4). The plot of $\log(M_t/M_\infty)$ versus $\log(t)$ graph revealed that each gels (Film-A and Film-C) have different diffusional coefficients, n (n = 0.16 and n = 0.24) related to release mechanism. This shows that the pores become larger as pH increases and Trp can diffuse faster out of the matrix, confirming the pore size controls the release rate of the encapsulated molecules.[36] When compared the profiles of Trp release of Film-A and Film-C at pH = 1.0 in 75% ethanol and 25% 1*M* trifluoroacetic acid mixture at ambient temperature, it was observed that both of the gels exhibited different release and solvent uptake (swelling rate) behaviors because of having sensitivity to pH of solvent. Film-A exhibited slightly faster Trp

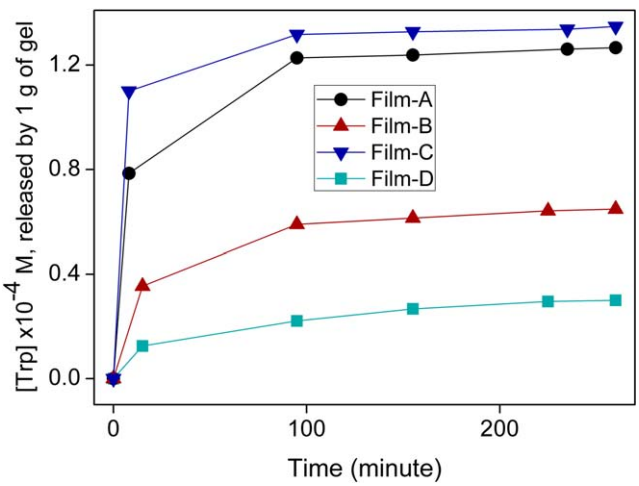

Figure 12. Trp release from polymer gels swollen in solvent mixture and then deswelled in water. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

release rate than that of Film-C (Supporting Information Figure S5). The liberation process of Trp from a solid carrier is essentially governed by both of matrix dissolution and diffusion, which are strictly connected with the physicochemical properties of the matrix itself. In particular, both hydrophilic/hydrophobic character of the matrix and the nature of interaction between Trp and the surface of the film play a key role on drug release behavior of hybrid gels. In the case of Film-A which contains APTES functional groups, hydrogen bonding interaction is weakened at low pH and this could probably explain its fast release kinetic.[37]

When Trp release in different solutions for each type of hybrid gels was compared, high amount of Trp release was obtained in *solution-3* (75% ethanol + 25% 1*M* trifluoroacetic acid) with pH 1.0, showing the weakening of interaction between Trp and functional groups at low pH values (Supporting Information Figure S6). On the other hand, Trp release from both Film-B and Film-D was almost same compared with those of the Film-A and Film-C in *solution-1* (75% ethanol and 25% water). This shows that interaction between Trp and functional monomer, APTES prevents releasing of Trp in solution with a pH of 6.64. Because two different precursors (like as, APTES and MTMOS) in Film-B and Film-D cause to alteration of the morphology, surface characteristics and properties of hybrid gels. Because the addition of methyltrimethoxysilane (MTMOS) causes to the decrease of surface silanol groups, which result in more hydrophobic surface. The view of gels after immersed into different solutions with different pH values was given in Supporting Information Figure S7. The modification with APTES changes dramatically the physicochemical properties of the silica matrix affecting, in particular, both reactivity and stability of the obtained materials in an aqueous medium. This aspect is very important for a drug-delivery system in which the matrix degradation could highly affect the sustained release.

CONCLUSION

The formation of hybrid polymer gel network was found to be completed within 40 minutes and revealed by following of fluorescence emission spectra of Trp. The swelling experiments showed that hybrid gel has the highest swelling degree in 75% ethanol–25% water mixture. The hybrid polymer gel containing PPG-ICPTS and MTMOS exhibited highest absorption of solvent compared with the other hybrid gel films. Swelling kinetic of hybrid gels was found to be pseudo-Fickian diffusion with different swelling rates. Hybrid polymer film with MTMOS as precursor exhibited the highest release of Trp at swelling equilibrium. Emission spectra obtained from the surface of polymer films showed that some amount of Trp was trapped in gel matrix, indicating insufficient swelling ratio of hybrid polymer gel films. Swelling behavior of hybrid gels in distilled water revealed that the smaller swelling ratio the greater rate of deswelling. Hybrid gel films exhibited slightly faster Trp release rate at low pH values since weak interactions occur between Trp and APTES compared with high pH values. This shows that the stimuli-responsive hybrid gel system controls the release of Trp, indicating the potential applications in the field of drug delivery.

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