# PEG-Hydrogel Coated Silica Aerogels: A Novel Drug Delivery System

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**Abstract:** A novel composite of silica aerogel-poly(ethylene glycol) PEG hydrogel was synthesized and its potential as a drug delivery system was investigated. The composite was synthesized by encapsulation of hydrophobic aerogels within PEG hydrogel via photoinitiated polymerization. Disks of aerogels were synthesized by the two step sol-gel method using tetraethylortosilicate (TEOS) as the silica precursor. After aging in ethanol, the alcogels were loaded with eosin-Y photoinitiator. The surface of eosin functionalized silica aerogels was then rendered hydrophobic using hexamethyldisilazane (HMDS) as the surface modification agent, and supercritical carbon dioxide ($scCO_2$) as the solvent. Hydrophobicity of aerogel was tuned by changing HMDS amount dissolved in $ScCO_2$ phase which resulted in the change of the contact angle between 0 and $128^o$. Hydrophobic or hydrophilic aerogels were then dipped into a PEG diacrylate prepolymer solution, and photopolymerization was carried out using visible light (514 nm). BET surface area and pore size distribution measurements showed that both hydrogel encapsulation and eosin-Y loading did not affect the pore structure of the aerogel. The potential of this composite as a drug delivery system was tested by Ketoprofen as a model drug. The results demonstrate that both drug loading capacity and drug release profiles could be tuned by changing the hydrophobicity of aerogels, and that drug loading capacity increases with decreased aerogel hydrophobicity while slower release rates are achieved with increased hydrophobicity from eosin functionalized aerogels. The effect of PEG concentration (0, 15 %, and 30 % w/w) in the prepolymer solution of the hydrogel coating on drug release rate from hydrophilic aerogel was also investigated. It was seen that as the PEG concentration increased, the drug release was retarded. The experimental results showed that drug release can be controlled with this novel aerogel-hydrogel composite system via changing hydrophobicity of the aerogel, and the concentration of the PEG in the hydrogel coating.

*Keywords: PEG hydrogel, aerogel, photopolymerization, encapsulation, Supercritical $CO_2$*

## INTRODUCTION

Silica aerogels are sol-gel derived materials with high surface areas, high pore volumes and low densities [1]. They are produced by supercritical drying of the gels obtained via hydrolysis and condensation reactions of a silicon alkoxide precursor such as tetraethylorthosilicate (TEOS) in a solvent. The properties of silica aerogels can be tailored by manipulation of reaction conditions and reactant concentrations during their synthesis and they can be produced as monoliths in any shape [2].The tunable surface and pore properties of porous silica aerogels make them promising candidates for the development of novel drug delivery devices [3,4]. In such an approach, the drug components may be oaded into the porous aerogels. A drug adsorbed on a hydrophilic silica aerogel can be released much faster than from its crystalline form [5]. The loading of the drug in the aerogel matrix can be controlled by the hydrophobicity of the aerogel surface.

Another important class of materials in pharmaceutics, biotechnology and medicine is hydrogels [6]. They have been prepared for use as drug carriers for the release of drugs, peptides and proteins due to their three dimensional, hydrophilic networks [7]. For example, polyethylene glycol (PEG) can be chemically crosslinked into hydrogels and used as reservoir

devices for the controlled delivery of smaller molecular weight drugs. PEG hydrogel has received significant attention, especially because of its non-toxic, non-immunogenic and hydrophilic character. Previous studies investigated the kinetics of PEG hydrogel formation, and diffusion of various drugs and/or proteins from these PEG hydrogels [5,8,9]. Hydrogels can also be designed to be responsive to various properties such as pH, temperature, concentration of a metabolite or electric field which may be utilized for different applications.

In this work, a novel composite material was synthesized by encapsulation of hydrophobic aerogels within PEG hydrogel via surface initiated photopolymerization [10]. Immobilized initiator on the surface of the aerogel started the formation of PEG diacrylate hydrogels on the surface. Eosin was used as the photoinitiator because of its spectral properties that perfectly suit its use as an initiating system for an argon ion laser [11]. Moreover, the drug delivery application of this composite was studied. The effects of hydrophobicity of aerogel and PEG diacylate concentration in the prepolymer solution of the hydrogel coating on the drug release rate were examined. Ketoprofen (3-benzoyl-R-methylbenzeneacetic acid) was chosen as a model drug due to its well-known solubility in $scCO_2$. Ketoprofen is widely used as non-steroidal, anti-inflammatory drug for the relief of acute and chronic rheumatoid arthritis and osteoarthritis, as well as for other connective tissue disorders and pains.

## MATERIALS AND METHODS

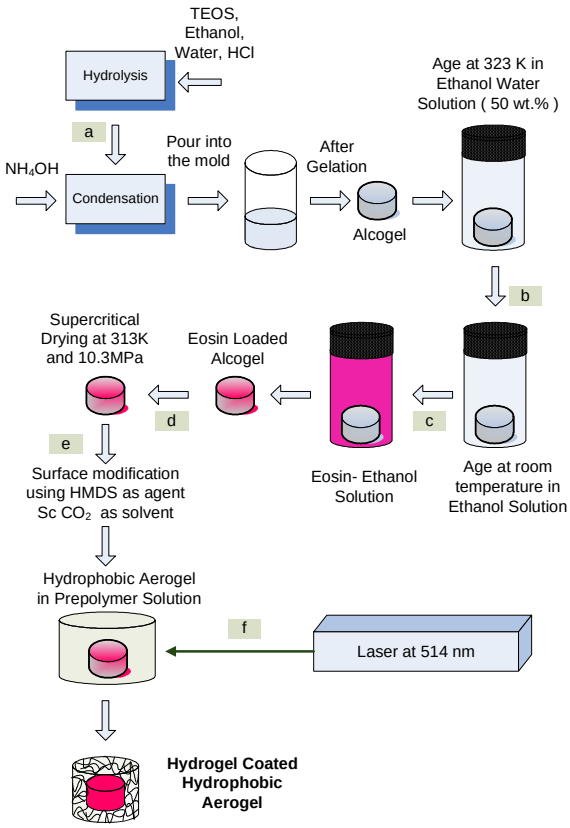


**Figure 1:** Schematic representation of the overall synthesis

**Materials.** For the synthesis of silica aerogels, TEOS (98.0 %) and $NH_4OH$ (2.0M in ethanol) were purchased from Aldrich, HCl from Riedel-de Haen (37%) and ethanol from Merck (99.9%). For the surface modification, HMDS was obtained from Alfa Aesar (98%). Carbon dioxide (99.998 %) was purchased from Messer Aligaz. For the hydrogel synthesis, Eosin Y (98%), 1-vinyl 2-pyrrolidinone (99+%), poly(ethylene glycol) diacrylate (PEG-DA) (MW ¼ 575 Da) were obtained from Aldrich. Triethanolamine (>99.5%) was obtained from Fluka. For the drug loading experiments, Ketoprofen (MW 254.29 g/mol) was also obtained from Aldrich. All chemicals were used as-received.

**Procedure of synthesis of silica aerogel and modifications**. Disks of aerogels with a diameter of 13.7 mm and a height of 3.3 mm were synthesized by the two step sol-gel method using TEOS as the silica precursor [12]. HCl and $NH_4OH$ were used as hydrolysis and condensation catalysts respectively (Fig. 2-a). The overall molar ratio of TEOS: Water: HCl:

$NH_4OH$ were kept constant at 1: 4: $2.44x10^{-3}$: $2x10^{-2}$ respectively. The alcogels were aged in ethanol-water (50 wt. %) solution at 323 K for 1 day and in pure ethanol at room temperature for 3 days (Fig. 2-b). The aim of the aging step was to improve the mechanical strength of the alcogels. After aging step, they were contacted with 2mM eosin-Y, a photoinitiator, in ethanol solution. The adsorption of eosin-Y on the surface of alcogel led to a reddish transparent composite of silica alcogel with eosin-Y (Fig. 2-c). The alcogels with eosin-Y were subsequently dried by supercritical $CO_2$ ($scCO_2$) at 313 K and 10.3 MPa (Fig. 2-d).

The hydrophilic and eosin functionalized aerogel formed in steps a through e, was rendered hydrophobic using supercritical fluid deposition technique. Hexamethyldisilazane (HMDS) was used as the surface modification agent, and $scCO_2$ as solvent at 20.68 MPa and 333.2 K (Fig. 2-e). The mechanism for surface modification was the replacement of the hydrogen atoms in the surface silanol groups by a hydrolytically stable organofunctional group (e.g. $Si-(CH_3)_3$) of HMDS. By varying the HMDS concentration in the vessel, aerogels with different degrees of hydrophobicity were obtained. Ketoprofen loading on aerogels was also performed with the $scCO_2$ deposition technique. The deposition was carried out at 333 K and 22 MPa of temperature and pressure conditions for 48 hours. For all loading experiments in $scCO_2$, ratio of the mass of aerogel to the mass of ketoprofen was kept constant as one. Finally, ketoprofen and eosin loaded hydrophobic aerogels were immersed in PEG-diacrylate prepolymer solution and photopolymerization was carried out using visible light (514 nm) for 3 min for each surface of the aerogels (Fig. 2-f). The hydrogel precursor was prepared with concent+rations of 225 mM triethanolamine, 25% (w/w) PEG diacrylate (MW = 575 Da), and 37mM 1-vinyl-2-pyrrolidinone (NVP). The solution was adjusted to pH 8 using HCl. Precursor solutions were filter sterilized using a 0.2 μm syringe Teflon filter. This step resulted in the formation of a cross-linked thin PEG hydrogel coating through surface-initiated polymerization around the hydrophobic aerogels. Drug release experiments were conducted at 310 K and under constant string at 100 rpm. The release medium was selected as 0.1 N HCl solution. At specific time periods, approximately 20 μl samples were taken using a micropipette (Eppendorf). Nanodrop spectrophotometer (Thermo Fisher Scientific Nanodrop 1000 spectrophotometer) was used to measure the concentration of the drug in these samples taken during the release experiments. The characteristic peaks of Ketoprofen were detected at 260 nm wavelength.

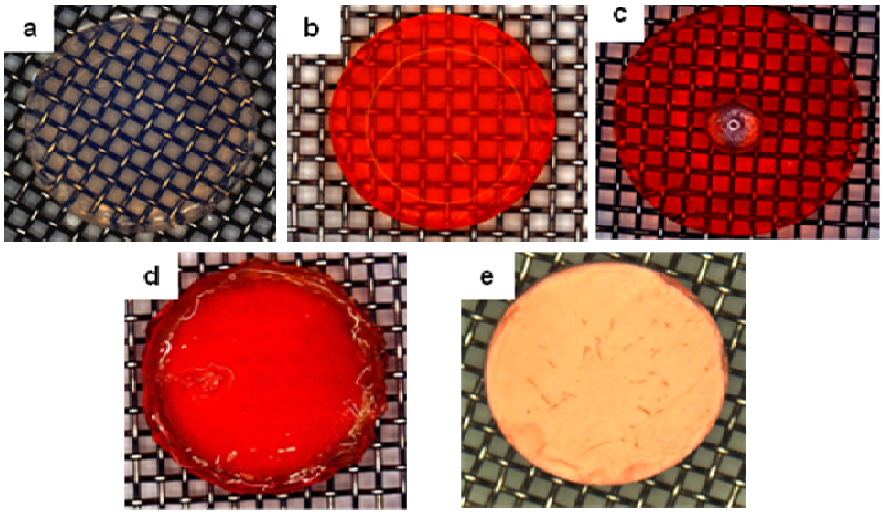


**Figure 3:** Images of a) the pure silica aerogel; b) eosin doped hydrophilic aerogel; c) water droplet on the Eosin doped hydrophobic aerogel; d) hydrogel coated hydrophobic aerogel; e) Ketoprofen loaded hydrophilic aerogel.

## RESULTS

It is observed from Figures 3-a and 3-b that the colorless transparent aerogel obtained a red color due to the presence of eosin within the aerogel structure. The figure also shows that eosin molecules were homogeneously distributed throughout the aerogel. After surface modification step, hydrophobicity of the aerogel was verified by placing a water droplet and measuring the contact angle on the surface of the aerogel (Fig. 3-c). The contact angle for the eosin modified hydrophobic aerogel was found to be $130^{o}$. Figure 3-d shows the image of a PEG hydrogel coated eosin functionalized hydrophobic aerogel. The thickness of the hydrogel coating was approximately 0.3 mm. Lastly, Figure 3-e displays the image of ketoprofen loaded hydrophilic aerogel.

The effects of the eosin loading and the surface modification step on the pore structure of the aerogel were investigated with the nitrogen adsorption analysis by Micromeritics ASAP 2020 surface analyzer. As seen in Table 1, the presence of eosin on the aerogel surface caused the BET surface area to decrease slightly with no appreciable changes in the average pore diameter. Further modification of the eosin functionalized aerogel surface with HMDS decreased the cumulative pore volume, surface area and also increased the average pore size slightly. This can perhaps be attributed to the presence of some bottleneck type pores which are blocked by Si-$(CH_3)_3$ groups. All samples exhibited similar pore size distribution and type H1 isotherm which indicates that the materials consist of compacts agglomerates of approximately uniform spheres of silica and such a network is not disrupted by eosin loading, surface modification, and PEG hydrogel coating.

BET surface area and pore size distribution measurements were also carried out for both non-coated and coated aerogels. The data showed that the surface area of the hydrophobic aerogel did not change after encapsulation with PEG hydrogel. Also, the isotherms and pore distributions of the two samples were nearly identical which indicate that the hydrogel coating was only restricted to the external surface of the monolithic disks and the water based prepolymer solution did not diffuse into the hydrophobic aerogel structure.

**Table 1:** Properties of Aerogel Composites After Each Step in Synthesis

| | BET Surface Area | BJH Desorption Cumulative Pore Volume | BJH Desorption Average Pore Radius |
|---|---|---|---|
| Pure Silica Aerogel | 926 $m^2/g$ | 2.9 $cm^3/g$ | 5.9 nm |
| Eosin Loaded Aerogel | 820 $m^2/g$ | 2.5 $cm^3/g$ | 6.0 nm |
| After HMDS Modification | 528 $m^2/g$ | 2.1 $cm^3/g$ | 6.4 nm |
| After Hydrogel Coating | 529 $m^2/g$ | 2.2 $cm^3/g$ | 6.7 nm |

It was previously shown by Smirnova et al. that the adsorption isotherm of Ketoprofen strongly depends on hydrophobicity of silica aerogel [13]. The loading of the hydrophobic aerogel is lower than that of the hydrophilic aerogel which is explained by the lack of surface OH groups, that provides the active sites for the hydrogen bonding in the case of hydrophilic aerogel. Our results are in good agreement with those already described in the literature (Table 2) and indicate that as a result of hexamethyldisilazane (HMDS) modification aerogels become hydrophobic that affect both drug loading capacity and also release rate.

**Table 2:** Results of contact angle and drug loading of different hydrophobic aerogels

| Ratio of HMDS/Aerogel (mg/mg) in $scCO_2$ | Contact Angle ($^o$) | Mass percentage of drug loading to the aerogel mass |
|---|---|---|
| 0 | 0 | 96 |
| 1.1 | 0 | - |
| 1.8 | 66 | 25 |
| 2.3 | 87 | 13 |
| 3 | 128 | - |
| 4.2 | 128 | 7 |

In order to determine the effect of the ratio of HMDS/aerogel (mg/mg) in $scCO_2$ on drug loading and the degree of hydrophobicity of aerogels, aerogels with different HMDS/aerogel (mg/mg) in $scCO_2$ ratios were prepared. The results showed that, as the ratio was increased from 0 to 4.2, hydrophobicity was also increased from 0 to 128 $^o$ (further increase in that ratio did not increase hydrophobicity further), while drug loading capacity decreased from 96 to 7 % (w/w) (Table 2). These percentages correspond to 41 mg and 4 mg total drug amount, respectively.

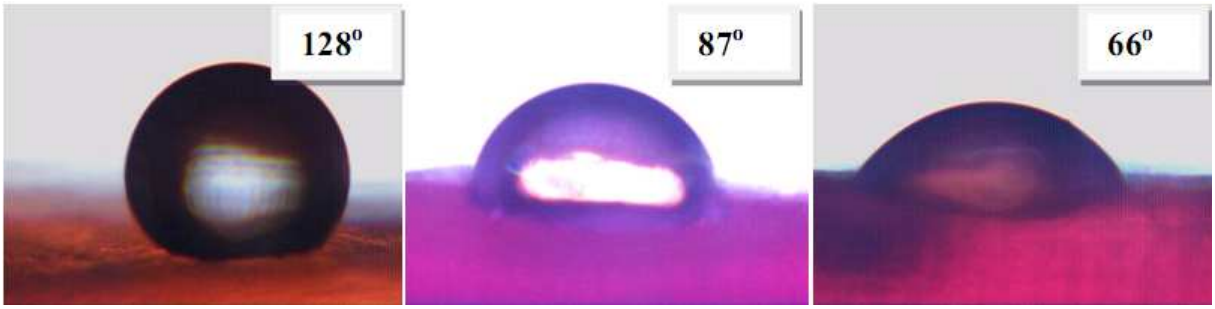


**Figure 4:** Image of water droplets on different hydrophobic aerogels

It should be noted that tuning of the hydrophobicity of the aerogels made it possible to synthesize aerogels with specific contact angels and thus (Figure 4).

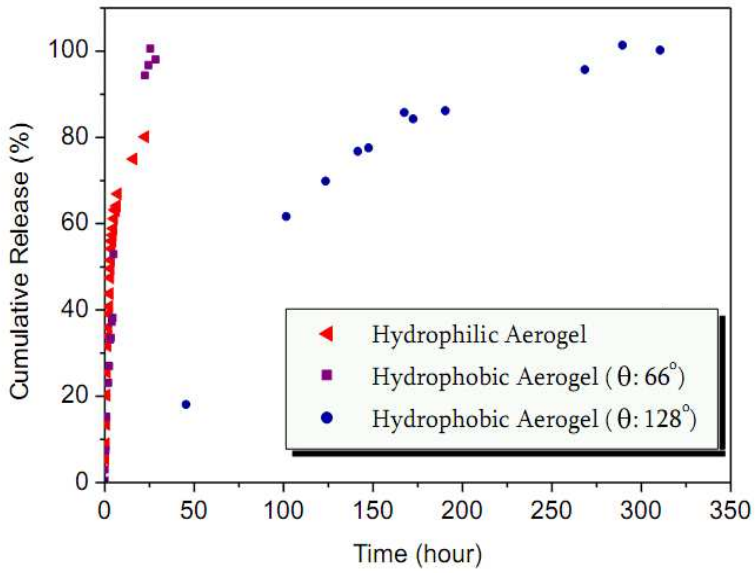


**Figure 5:** Release behavior of Ketoprofen from different hydrophobic aerogels in 100 ml of 0.1 N HCl solution at 37 $^{o}$C and under constant stirring at 100 rpm

The effect of hydrophobicity of the aerogel on drug release was analyzed using the aerogel without the hydrogel coating. The result of the release experiments demonstrated that immediate or sustained release of ketoprofen from non-coated aerogel was observed depending on the degree of hydrophobicity of aerogel. As shown in Figure 5, the drug release can be controlled by changing the hydrophobicity of the aerogel. As aerogels became more hydrophobic, the release rate gets slower. For hydrophilic aerogels, the release was completed nearly in 10 hours. However, for aerogels with contact angle 66$^{o}$, the release was completed in nearly 24 hours (Fig. 5). When the hydrophobicity of aerogel increased further, it was seen that release rate slowed further, too. Thus, alteration of hydrophobicity of the aerogel caused the release rate to decrease because the penetration of water based release medium through the aerogel became difficult with increased hydrophobicity.

Beside these, it was observed that the hydrophilic aerogel lost its disk-shape during the release experiments as a result of the matrix erosion which occurred. On the other hand, all hydrophobic aerogels preserved their original shapes during the experiment. The absence of matrix erosion was an indication that the release was governed mainly by diffusion, where zeroth-order release kinetics was not observed for hydrophobic aerogels. It should be also noted that ketoprofen loading capacity decreased down to 7 % (w/w) for the highest hydrophobicity conditions where the contact angle was measured as 128$^{o}$. 7 % by weight corresponds to nearly 5 mg for the typical disk shaped aerogels used in this study. However this amount can be increased up to 40 mg by decreasing the hydrophobicity of the aerogels .

The release profiles from hydrogel coated aerogels were also investigated. Hydrogel coating was used as a way to control the release rate from aerogels. The effect of hydrogel coating was analyzed by altering the concentration of the dimethacrylated PEG macromers which influence gel crosslinking density. Because the crosslink density affects the available free volume in the matrix for the movement of the drug molecules, the release rates from coated hydrogel differs as the PEG concentration of the hydrogel changes.

Figure 6 shows ketoprofen release rates from non-coated aerogel, and coated aerogels with hydrogels which have two different PEG concentrations; 15 % and 30 % by weight. As it is seen, the rate is the largest for non-coated hydrogel. As PEG concentration in the hydrogel

coating increased, the release was hindered. As it is expected, the drug molecules cannot diffuse directly into the release media from the aerogel external surface due to the hydrogel coating. The porosity of hydrogel which depends on the crosslink density affects the diffusion coefficient of the drug in the hydrogel, and thus affects the release rate of drug. In these experiments, all aerogels included nearly the same amount of drug which is around 40 mg. 80% of cumulative release of that drug was reached for coated and non-coated samples which means drug did not entrapped in the hydrogel layer. This could be explained by the low molecular weight (MW: 259 g/mol) of the ketoprofen.

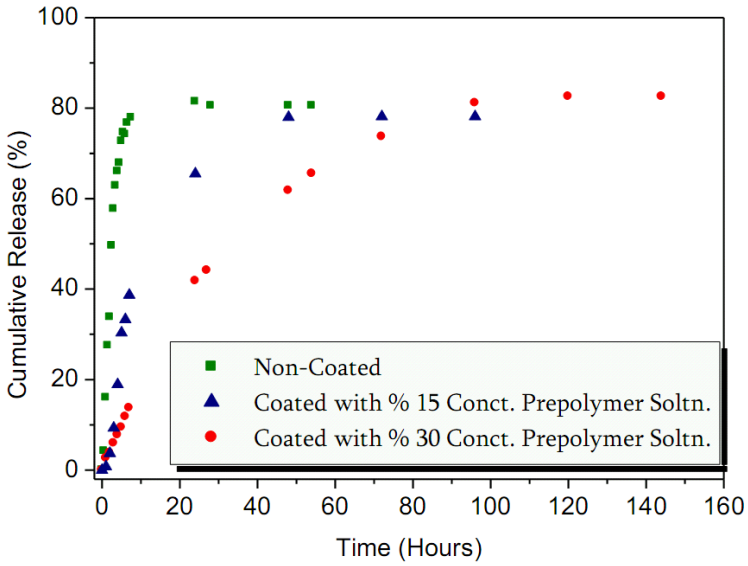


**Figure 6:** Release behavior of Ketoprofen from coated hydrophilic aerogels in 100 ml of 0.1 N HCl solution at 37 $^{o}$C and under constant string at 100 rpm

It must be pointed out that the hydrogel coating effect was examined by using hydrophilic aerogels and not hydrophobic ones, since the hydrogel coating for the most hydrophobic aerogel did not decrease the release rate further. However, the hydrogel coating effect can be used to retard the release rate for the hydrophobic aerogels with contact angle less then 128 $^{o}$. Additionally, it may be possible obtain subsequent release profiles for drugs or proteins with various hydrophobicities from this aerogel-hydrogel composite through loading of additional drug or protein into the PEG hydrogel structure. Furthermore, the release rates may be extended or reduced by using PEG polymer with different molecular weights, and by controlling the permeability of the hydrogel layer.

## CONCLUSIONS

A novel composite of silica aerogel and PEG hydrogel was synthesized and its potential as a drug delivery system was investigated. Aerogels were synthesized by the two step sol-gel method using tetraethylortosilicate (TEOS) as the silica precursor. The alcogels were contacted with a solution of eosin-Y, a photoinitiator, dissolved in ethanol. After the drying procedure with $scCO_2$, disk shaped Eosin-Y functionalized aerogels were produced. Then, silica aerogels were rendered hydrophobic using hexamethyldisilazane (HMDS) as the surface modification agent, and $scCO_2$ (supercritical carbon dioxide) as solvent. Hydrophobicity of aerogel was tuned by changing HMDS amount dissolved in $scCO_2$ phase which changes the contact angle between 0-128 $^{o}$. For hydrogel coating, hydrophobic or hydrophilic aerogels were then dipped into a PEG diacrylate prepolymer solution, and photopolymerization was carried out using visible light (514 nm).

It is important to preserve the both aerogel and hydrogel structural properties during the synthesis. Thus, possible changes in the aerogel structure though synthesis processes were investigated by using nitrogen adsorption-desorption isotherms, BET surface area and BJH pore size calculations. As a result, two different structure such hydrophilic, wet network which is hydrogel and hydrophobic, dry network which is aerogel were successfully combined without losing their structural property. Additionally, the drug delivery properties of this composite were studied. The effects of hydrophobicity of aerogel and PEG concentration of the hydrogel coating of hydrophilic aerogels on the drug release rate were examined using Ketoprofen as a model drug.

It was seen that the drug loading capacity increases with decreased aerogel hydrophobicity while slower release rates are achieved with increased hydrophobicity. As the polymer concentration increased (0, 15 %, and 30 % by weight), the drug release was retarded. The experimental results show that the by using aerogel-hydrogel composite system, drug release can be controlled via changing hydrophobicity of the aerogel, and the concentration of the PEG in the hydrogel coating.

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## REFERENCES

[1] STOLARSKI, M., WALENDZIEWSKI, J., PIANK, M.S.B., Applied Cat. A., Vol. 177, **1999**, p. 139
[2] DORCHEH, A.S., ABBASI, M.H., J. Materials Processing Tech., Vol. 199, **2008,** p. 10
[3] SIMIRNOVA, I., MAMIC, J., ARLT, W., Langmuir, Vol. 19, **2003**, p. 8521
[4] GORLE, B.S.K., SMIRNOVA, I., MCHUGH, M.A., J. Supercrit. Fluids, Vol. 48, **2009**, p. 85
[5] LOWMAN, A.M., PEPPAS, N.A., Macromolecules, Vol. 30, **1997**, p. 4959
[6] BROMBERG, L.J., Apply. Polym. Sci., Vol. 59, **1996**, p. 459
[7] PARK, H., PARK, K., In: OTTENBRITE RM, HUANG SJ, PARK K (ed) Hydrogels and Biodegradable Polymers for Bioapplications. ACS Symposium Series 627, American Chemical Society, Washington DC, **1996**
[8] PEPPAS, N.A., BURESA, P., LEOBANDUNGA, W., ICHIKAWAB, H., European Journal of Pharmaceutics and Biopharmaceutics, Vol. 50, **2000**, p. 27
[9] KIZILEL, S., PEREZ-LUNA, V.H., TEYMOUR, F., Macromol. Theory Simul., Vol. 15, **2006**, p. 686
[10]KIZILEL, S., Langmuir, Vol. 20, **2004**, p. 8652
[11]VALDES-AGUILERA, O., PATHAK, C. P., SHI, J., WATSON, D., NECKERS, D. C., Macromolecules, Vol. 25, **1992**, p. 541
[12]BRINKER, C.J., KEEFER, K.D., SCHAEFER, D.W., ACHLEY, C.S., J. Non-Cryst. Solids, Vol. 48, **1982**, p. 47
[13]SMIRNOVA I., SUTTIRUENGWONG S., SEILER M., ARLT W., Pharm Dev Technol., Vol. 9(4), **2004**, p. 443