

# Controlling Drug Release of Sol–Gel Encapsulated Persantin and Propranolol by Surface Interactions

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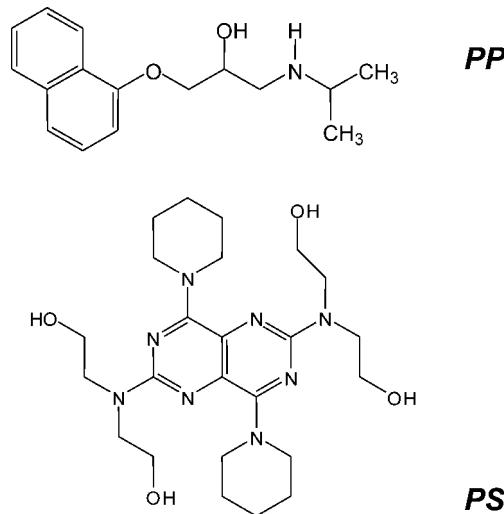
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Two drug molecules, Propranolol and Persantin, have been encapsulated by a sol–gel process in an organic–inorganic hybrid matrix by *in situ* self-assembly. The synthesis parameter, compositions, and pH values in the sol–gel synthesis control the dissolution of the drugs and pore size and distribution of the gels. The noncovalent host–guest interaction can be tailored to control the release kinetics by appropriate choice of an organic group in the hybrid matrix. The surface interactions of the drug as well as the diffusion barriers of the matrix control the release kinetics of the drug molecules. The higher surface area of spray dried microparticles with molecularly dispersed drug molecules enhances the dissolution process.

## Introduction

The formation of porous materials is an ongoing quest because of the numerous applications of such materials in separation science, chiral catalysis, and pharmaceuticals.<sup>1</sup> Sol–gel derived silica xerogel has been studied as a carrier material for various drugs, peptides, and proteins.<sup>2</sup> Bioactive agents can be incorporated into silica xerogel either by adsorbing drug onto the surface of the heat-treated silica xerogel<sup>3</sup> or by adding the drug during the sol–gel manufacturing process.<sup>4,5</sup> The self-assembly of organized nanoscopic structures is of great interest in both colloidal and material science.<sup>6</sup> Solid materials containing chemical functionalities are created using the molecular imprinting technique by employing templates with the help of covalent and noncovalent interactions.<sup>7</sup> In a recent report, such noncovalent interactions of drug molecule encapsulated in hybrid silica gel were investigated by high-resolution 2D solid state



**Figure 1.** Molecular structure of Propranolol (PP) and Persantin (PS).

NMR spectroscopy.<sup>8</sup> In this study we report the development of organic–silica based drug carriers by sol–gel techniques for the controlled release of drug. Two drugs, Persantin and Propranolol (Figure 1), were used as model substances to evaluate the possibilities to control the drug release rate from evaporation induced self-assembled gels and spray dried gels. Controlled release over an extended duration is highly beneficial for drugs that are rapidly metabolized and eliminated from the body after administration. All controlled release systems aim to improve the effectiveness of drug therapy. This improvement can take the form of increasing therapeutic activity compared to the intensity of side effects and reducing the number of administrations required during the treatment. One of the aims of the study was to develop a controlled release system for Propranolol and Persantin which was achieved by imprinting the drug into a sol–gel derived silica network.

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The engineering of porosity in common materials such as silica is an area of technological and scientific interest.<sup>9</sup> The development of porous materials with large specific surface area is currently an area of extensive research, particularly with regard to potential applications in areas such as adsorption, chromatography, catalysis, sensor technology, and gas storage.<sup>10</sup> Microporous cavities of zeolites and other engineered porous materials have been used as nanosized reaction vessels<sup>11</sup> or hosts in which to assemble semiconductor clusters,<sup>12</sup> organic molecules,<sup>13</sup> and even molecular wires.<sup>14</sup> Brinker et al. have done some pioneering works on the synthesis of porous amorphous silicas using the sol–gel approach.<sup>15</sup> They have found that in organic template derived amorphous silicas, the nature of template–matrix interactions and the subsequent processing dictate the final pore morphology. The pore structure in silica gel is an important factor especially in controlling the function as a drug release system.<sup>16</sup> The purpose of this study is to investigate the influence of synthetic control parameters on drug release kinetics and porosity of the sol–gel materials.

## Experimental Section

Propranolol, DL-1-(isopropylamino)-3-(1-naphthoxy)-2-propanol hydrochloride, is a colorless crystalline powder with molecular weight of 295.8 g/mol that was purchased from Sigma-Aldrich Chemie GmbH (Steinheim, Germany) and was used as received. Propranolol hydrochloride (PP) is a beta-adrenergic antagonist (beta-blocker) used extensively in the treatment of cardiovascular disorders such as hypertension, cardiac arrhythmias, and angina pectoris. It is weakly basic with a  $pK_a$  value of 9.2,<sup>17</sup> and it has a nearly pH-independent solubility over a physiological pH range (1–7). Persantin, 2-[[3-[bis(2-hydroxyethyl)amino]-5,10-bis(1-piperidyl)-2,4,7,9-tetrazabicyclo[4.4.0]deca-2,4,7,9,11-pentaen-8-yl]- (2-hydroxyethyl)amino]ethanol, is a yellow crystalline powder, with molecular weight of 504.6 g/mol. Persantin (PS) is a coronary vasodilator and is also used to prevent platelet aggregation after heart valve disease. It is monobasic with a  $pK_a$  value of 6.4.<sup>5</sup> Persantin is sparingly soluble in pure water but readily soluble in organic solvents such as chloroform, ethanol, and acetone. Quaternary monomer (Q monomer) tetraethylorthosilicate (TEOS), tertiary monomers (T monomers) ethyltriethoxysilane (ETS) and phenyltriethoxysilane (PhTS), and binary monomer diphenyldiethoxysilane (DPhDS) were purchased from ABCR GmbH & Co. KG (Karlsruhe, Germany) and were used as received.

**Synthesis. Gels without T Monomer.** In a typical synthesis, Propranolol, PP (0.44 g), was dissolved in a mixture of water (4.5 mL) and ethanol (5.8 mL). TEOS was added to this solution. The solution was stirred while adding 1.0 M HCl (0.1 mL), and the pH

was varied by adding NH<sub>3</sub> (aq). The sol was stirred for 24 h at room temperature and after that subjected to evaporation induced self-assembly (EISA) at 323 K in an open vessel for 24 h followed by drying at 323 K for constant weight. The final relative molar ratios and pH values of the sol formulations are given in Table 1. All oven-dried gels were treated in a ballmill for 3 min at 200 rpm to obtain a similar particle size distribution.

**Gels with T monomer.** To a mixture of PP, ethanol, and water were added the two precursors TEOS and ETS (or PhTS). The 1.0 M HCl was added while stirring the mixture, and after the hydrolysis, the pH was adjusted with the addition of ammonia. The sol was stirred for 24 h at room temperature and after that subjected to evaporation induced self-assembly (EISA) at 323 K in an open vessel for 24 h followed by drying at 323 K for constant weight. The final relative molar ratios and pH values of the sol formulations are given in Table 1. All oven-dried gels were treated in a ballmill for 3 min at 200 rpm to obtain a similar particle size distribution.

**Gels with Spray Drying (SD).** The sols were prepared in the same way as before, but spray drying was used for preparing the gels. The hydrolyzed silica sol was spray dried with a mini spray dryer (B-290, Büchi Labortechnik AG, Switzerland). The spray drying process parameters were inlet temperature, 393 K; pump, 20–30%; aspirator capacity, 90–95%, and spray flow rate, 5 mL/min; a nozzle of size 0.77 mm was used.

**Gels with Persantin.** The sols were prepared with Persantin instead of Propranolol in the same way as before and spray dried with conditions similar to those described above. Quaternary monomer TEOS and tertiary monomer PhTS (or binary monomer DPhDS) were silica sources. Final relative molar ratios and pH values of the sol formulations are given in Table 1.

**Instrumental.** All dissolution tests were performed at 310 K and 100 rpm under sink conditions in a VK 7010 dissolution bath with an autosampler (VanKel industries, NJ, U.S.A.), and 900 mL of double-distilled water was used as a dissolution medium for PP, and 900 mL of solution of 0.1% HCl was used as a dissolution medium for PS. The gel samples were packed in a gelatine capsule at approximately 50 mg drug per capsule. The drug concentration in the dissolved samples was measured by UV/vis spectrometry at 289 nm for Propranolol hydrochloride and 402 nm for Persantin.

Nitrogen adsorption experiments were carried out on a Micromeritics ASAP 2010. The samples were dehydrated for 24 h under vacuum at 373 K before adsorption. The microscopic analysis by scanning electron microscopy was carried out in a high resolution JEOL 840 instrument.

For ICP-OES analysis 50 mg of the sample are suspended in 75 mL of 0.1 N HCl solution and stirred for 24 h. The filtrate was analyzed by ICP-OES after diluting to 100 mL. CertiPUR Si-Standard (998 ± 5 mg/L SiO<sub>2</sub> in 0.5 mol/L NaOH, Merck) was used for calibration.

## Results

**Silica Gel Formulations from a Single Precursor.** The release of Propranolol from TEOS gels is shown in Figure 2. Silica gels made at different pH values from 0.5 to 5.5 in the presence of PP show a strong pH dependence in release kinetics. Around 60 wt % of the drug was released within 22 h, for gels synthesized between pH 1.1 and 2.5. A fast initial release occurs for gels synthesized at pH values 0.5 and above 3.0, whereas a retarding effect is observed in gels synthesized at pH value around 2.0. At pH values of 0.5 and above 3.0, the initial burst accounted for approximately 70%. The release kinetics of Propranolol from the gels was evaluated using the equation<sup>18</sup>  $M/M_0 = kt^n$ , which describes

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Table 1. Total Molar Ratios, pH Values before Gel Formation, and Gelation Times

Gels Prepared with Propranolol: Relative Molar Ratios of Gels with only Q Monomer							
gel	TEOS	H <sub>2</sub> O	ethanol	HCl	PP	<i>t</i> <sub>s</sub> (h)/pH	drying method
TEOS1	1	4.9	1.95	0.0098	0.029	24/0.5	OD
TEOS2	1	4.9	1.95	0.0098	0.029	24/1.1	OD
TEOS3	1	4.9	1.95	0.0098	0.029	24/1.5	OD
TEOS4	1	4.9	1.95	0.0098	0.029	24/2.0	OD
TEOS5	1	4.9	1.95	0.0098	0.029	24/2.5	OD
TEOS6	1	9.8	3.9	0.0039	0.029	96/3.0	OD
TEOS7	1	4.9	1.95	0.002	0.029	24/5.5	OD
TEOS8	1	4.9	1.95	0.0098	0.000	24/0.5	OD

Gels Prepared with Propranolol: Relative Molar Ratios of Gels with T Monomer ETS								
Gel	TEOS	ETS	H <sub>2</sub> O	ethanol	HCl	PP	<i>t</i> <sub>s</sub> (h)/pH	drying method
ETS1	1	0.20	5.88	2.34	0.0024	0.035	24/1.2	OD
ETS2	1	0.33	6.53	2.60	0.0026	0.039	24/1.2	OD
ETS3	1	0.10	5.39	2.14	0.0323	0.032	24/1.2	SD
ETS4	1	0.20	5.88	2.34	0.0353	0.035	24/1.2	SD

Gels Prepared with Propranolol: Relative Molar Ratios of Gels with T Monomer PhTS								
Gel	TEOS	PhTS	H <sub>2</sub> O	ethanol	HCl	PP	<i>t</i> <sub>s</sub> (h)/pH	drying method
PhTS1	1	0.10	5.38	2.14	0.0323	0.032	24/1.0	OD
PhTS2	1	0.20	5.89	2.35	0.0354	0.035	24/1.0	OD
PhTS3	1	0.10	5.38	2.14	0.0323	0.032	24/1.0	SD
PhTS4	1	0.20	5.89	2.35	0.0354	0.035	24/1.0	SD

Gels prepared with Presantin: Relative Molar Ratios of Gels with T Monomer PhTS/DPhDS								
gel	TEOS	PhTS	H <sub>2</sub> O	ethanol	HCl	PS	<i>t</i> <sub>s</sub> (h)/pH	drying method
PhTSPS1	1	0.33	6.51	2.59	0.1569	0.026	24/0.5	SD
PhTSPS2	1	0.10	5.38	2.14	0.1298	0.022	24/0.5	SD

Gels prepared with Presantin: Relative Molar Ratios of Gels with T Monomer PhTS/DPhDS								
gel	TEOS	DPhDS	H <sub>2</sub> O	ethanol	HCl	PS	<i>t</i> <sub>s</sub> (h)/pH	drying method
DPhDSPS1	1	0.20	5.88	2.34	0.1417	0.024	24/0.5	SD
DPhDSPS2	1	0.10	5.38	2.14	0.1298	0.022	24/0.5	SD

the release of drugs from various geometrical forms and diffusion mechanisms. The dissolution kinetics of Propranolol corresponds to diffusion controlled release ( $n = 0.30$ – $0.43$ ) for silica gels prepared at pH values around 2, as shown in the inset of Figure 2. The release parameters  $k$  and  $n$  are illustrated in Figure 3. For the pH values in the range 0.5–3.0, the kinetic release parameters  $k$  and  $n$

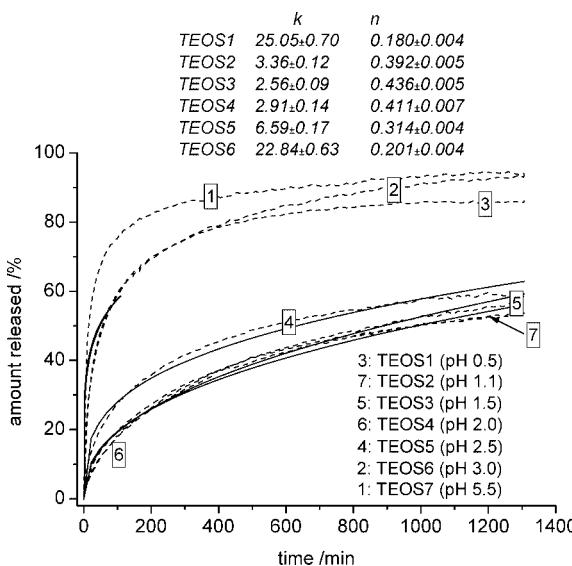


Figure 2. Drug release profiles of Propranolol from TEOS gels. Solid lines are fits (see text).

presume a minimum and a maximum value, respectively. This corresponds to release curves with the smallest curvatures. The release curvature increases below and above this intermediate acidic pH values in the synthesis.

**N<sub>2</sub> Sorption Studies.** N<sub>2</sub> sorption studies have been carried out for the characterization of the porosity of gels and are shown in Figure 4. The N<sub>2</sub> sorption isotherm of the Gel TEOS8, which is prepared in the absence of drug, is of type I, indicating a microporous material. The BET surface area and the micropore volume are 304 m<sup>2</sup>/g and 0.149 cm<sup>3</sup>/g,

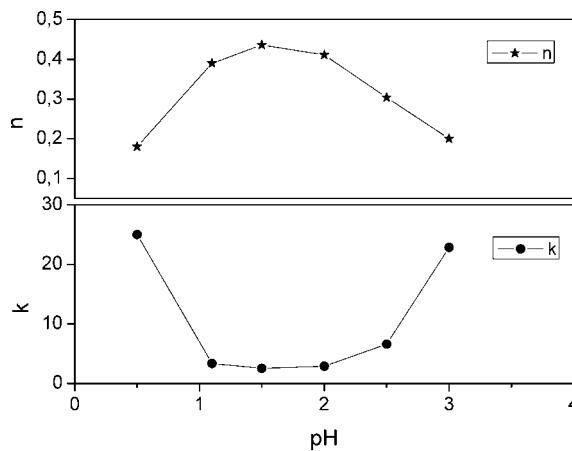
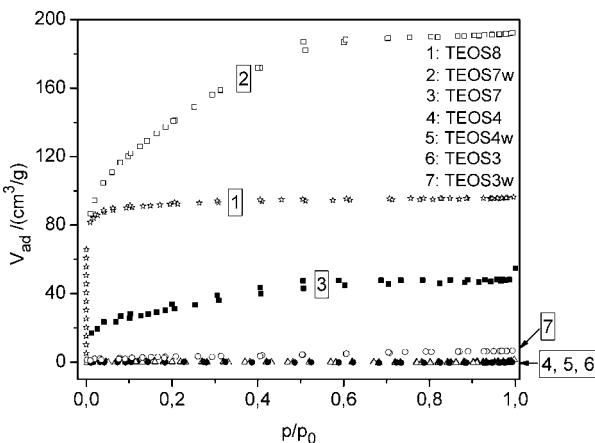


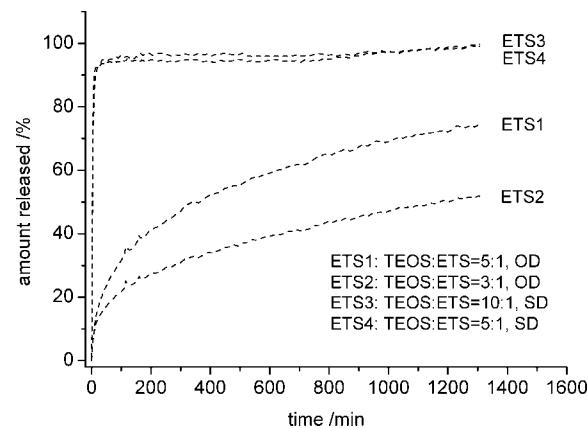
Figure 3. pH dependence of kinetic release parameters of TEOS based gels.



**Figure 4.**  $\text{N}_2$  sorption isotherms of various TEOS gels before and after extraction (w).

respectively. The micropore size distribution is derived from physisorption isotherm data using the Horvath–Kawazoe method and found to be in the range of 0.2–0.4 nm. Although the Gel TEOS4 and Gel TEOS3 released a considerable amount of drug within 22 h as indicated by the dissolution rate test (DRT) graph, no significant porosity and hence surface area are observed in these materials. The nitrogen sorption capacity of Gel TEOS7 is clearly higher after the release. The untreated sample shows a small specific surface of  $114 \text{ m}^2/\text{g}$ , while the washed sample exhibits a very high specific surface area of  $500 \text{ m}^2/\text{g}$ . Gel TEOS7 was synthesized at pH 5.5, and porous silica architectures were formed with a mixture of micro- and mesopore contributions to the total porosity of washed gel TEOS7w. The DRT graph clearly confirms that more than 90% of the loaded drug was released during the 22 h study. The pores emptied after the drug release are accessible to nitrogen adsorption and generate a high surface area material.

The faster release from the most acidic gels (pH 0.5) is interpreted as follows. The silica gel matrix is protonated at very acidic pH values in addition to the presence of protonated PP molecules. Therefore, at pH values below 1.5, protonated Propranolol molecules are incorporated in a protonated silica matrix, which leads to a stronger tendency for dissolution than in the pH ranges of neutral or negatively charged silica. Charge neutrality at low pH can then be rationalized by the inclusion of the desired number of counterions (e.g.,  $\text{Cl}^-$ ), resulting in a salt-in-salt inclusion model. Retarded release from the gels that is observed near the charge matching point of silica is interpreted as follows. Gels made at pH values close to 2.0 show no sorption capacity, although they have released an appreciable amount of drug during the 24 h extraction process. This is a clear indication that the pores formed at these pH values are much smaller after release than before. This observation is also supported by the diffusion controlled release mechanism indicated by the parameter  $n$  (value close to 0.43).<sup>5</sup> At higher pH values, larger pores are formed, which also facilitates faster release. At this point, it is impossible to predict the role of drug molecules in the evolution of silica networks.



**Figure 5.** Drug release profiles of Propranolol from oven-dried and spray dried ethyl substituted gels.

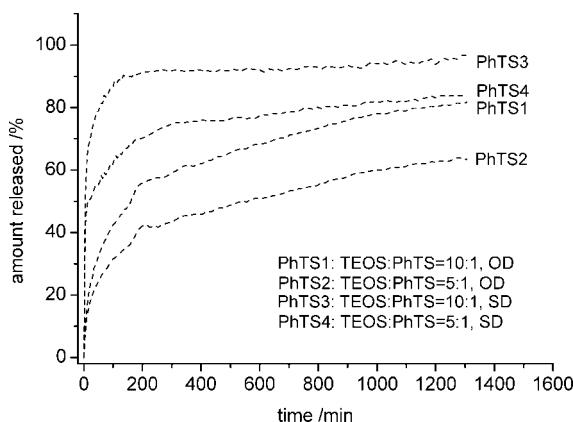
One important unanswered question is exactly what silica species are present during the formation of silica gels and what the role of drug molecules in the generation of the porous structure. These issues will be discussed in the context of hybrid gels.

**Silica Gel Formulations from Two Precursors.** (a) *Influence of Composition.* The release profiles of gels made with different TEOS:ETS ratios are compared in Figure 5. A high level of ethyl substitution in hybrid gel (ETS2) leads to a decrease in the drug release compared to a low substituted gel (ETS1). Due to the presence of ethyl groups in the surface, the gel particles are hydrophobic, and the solvent's ability to dissolve the drug molecule from the pores decreases with an increase in the ETS level. At the very acidic pH, the hydrophobic effect is masked by the salt-like character of the system.

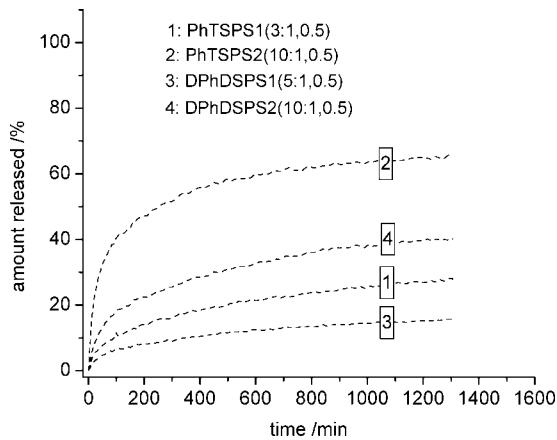
(b) *Influence of Drying Method.* The release profiles of gels made with different drying conditions are shown in Figure 5. The oven-dried gels (ETS1 and ETS2) show retarded drug release compared to spray dried gels (ETS3) and (ETS4). The two gels (ETS1 and ETS4) with the same TEOS:ETS ratios and different drying conditions show quite a different drug release patterns. Hence, the drying condition causes dramatic changes in the release profile of drug. Another precursor used in this study was PhTS, which exhibits similar release behaviors compared to ETS gels. The release profiles of gels made with different TEOS:PhTS ratios are shown in Figure 6. Here the composition influence is again very strong, and higher amount of T precursors in the hybrid gel leads to retarded drug release. Faster drug release was again observed for gels which were prepared by spray drying.

(c) *Drug Release from Persantin Incorporated Gels.* Different aromatic precursors, PhTS and DPhDS, were used for the preparation of aromatic substituted hybrid silica gel microparticles in presence of the drug molecule Persantin by spray drying. The release profiles of PS from gels made with different TEOS:PhTS ratios are compared in Figure 7. A high level of PhTS in the hybrid gel leads to a decrease in the drug release for gels prepared at a pH value around 0.5. What is more striking is that the addition of phenyl groups induces a strong retarding effect in the hybrid gel. Both the DPhDS hybrid gels show very strong retarded drug

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**Figure 6.** Drug release profiles of Propranolol from oven-dried and spray dried phenyl substituted gels.



**Figure 7.** Drug release profiles of Persantin from aromatic substituted spray dried gels.

release. When the substitution ratios are similar, a significant influence on the release of PS was observed between PhTS and DPhDS substituted gels. No burst release was observed for these aromatic systems. The retarded releases from the aromatic substituted gels are attributed to the hydrophobic effect and/or the preferable interactions between the aromatic groups ( $\pi$ - $\pi$  interactions).

(d) *Surface Studies by SEM.* The microscopic analysis by scanning electron microscopy was carried out on microparticles to obtain information about the morphology and to evaluate their shape, size, and surface. The SEM micrographs of phenyl and diphenyl substituted gels are given in Figure 8. The SEM micrographs reveal the formation of hollow spheres upon spray drying and the agglomeration of nearly uniform sized particles before and after the drug dissolution. The spherical particles have an average diameter of around 3  $\mu$ m. The micrograph also shows that a mixture of buckled spherical particles and fine spherical particles are formed during spray drying. A mixture of spray dried particles was generated as a result of a broad size distribution of the droplets that are present in a spray drying process. Dimpled spherical particles were formed as a result of buckling of the shell during which capillary force driving the shell deformation overcomes the steric or electrostatic forces stabilizing against aggregation.<sup>19</sup> The microparticles after drug dissolution show no collapse of structure. However, there is a significant change in the surface morphologies as

can be clearly seen in the amplified micrograph of Gel PhTSPS2w. The appearance of a rough surface indicates the dissolution of salt and subsequent degradation of the particles. The micrograph of Gel DPhDSPS2 shows the formation hollow spheres. The microparticles show no collapse of shell structure after drug dissolution. The size distribution of EISA gels is in the range of hundreds of micrometers. Changes of drug release rates are not influenced by matrix erosion effects. Less than 1 ppm of Si is detected by ICP-OES in the solution after drug extraction of gels synthesized at the most acidic pH values, and Si dissolution further decreases at higher pH.

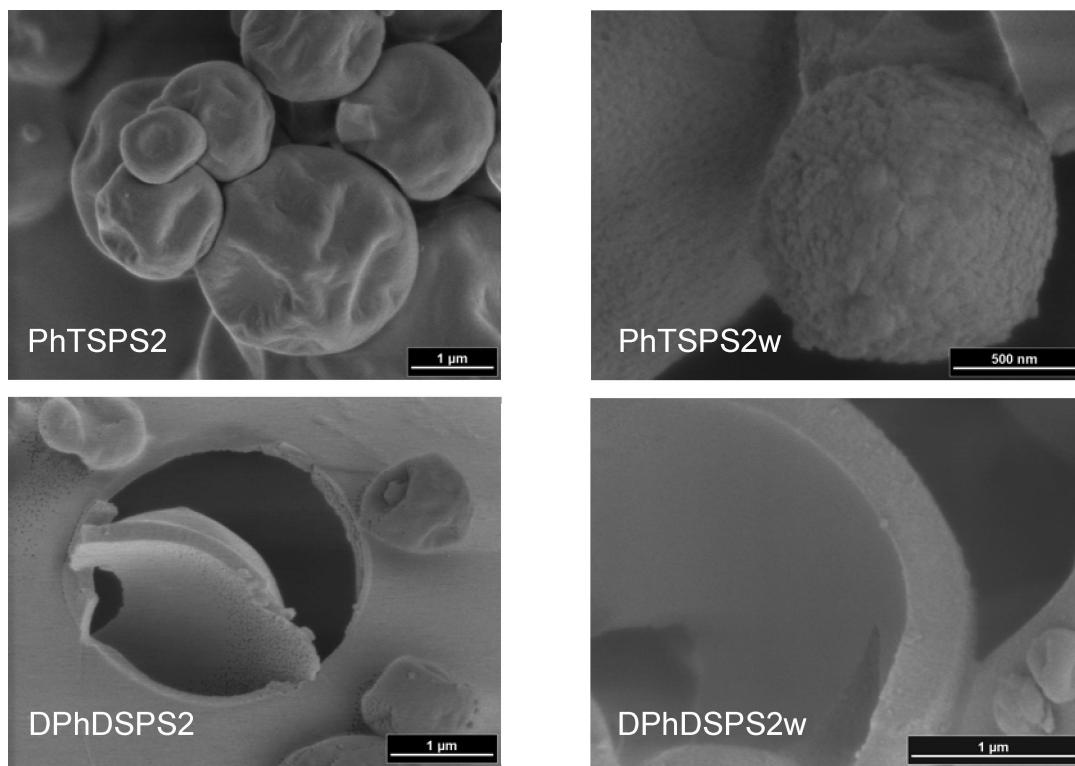
## Discussion

In a self-assembled sol-gel synthesis in the presence of drug molecules, the nature of guest-host interactions and pore structures is dictated by the synthetic pH values. Three different pH regimes can be rationalized to understand the pH effects. Figure 9 illustrates the pH regimes in which porous silica gels can be formed. The first regime is at pH values below 1.5, the second is between 1.5 and 2.5, and the last is above 2.5. Three different drug-matrix interaction pathways can be identified in the above regimes:  $D^+X^-M^+$ ,  $D^+M^-/M^0$ , and  $D^0/D^+M^-$ , where D is the drug, M is the matrix, and X is the mediating ion (e.g.,  $Cl^-$ ). In the  $D^+X^-M^+$  case, both the drug and matrix are protonated and occur at pH values below 1.5. In this regime, protonated drug molecules are incorporated in a protonated silica matrix, which leads to a stronger tendency for dissolution. Charge neutrality at low pH can then be rationalized by the inclusion of the desired number of counterions (e.g.,  $Cl^-$ ). At the charge-matching regime, the overall charge between drug and matrix are matched ( $D^+M^-/M^0$ ). In this regime, a favorable interaction between drug and matrix exists. The  $D^0/D^+M^-$  case applies at higher pH values where the drug molecules are either neutral or charged depending on the  $pK_a$  value of the drug, while the matrix is negatively charged. The excess of negative matrix charge is then compensated by  $H_3O^+$ . Larger pores are formed in this pH region due to the inclusion of hydronium ions in a solvate environment. The larger pores facilitate faster drug release.

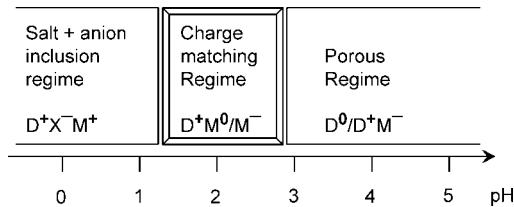
The charge matching regime is controlled by the isoelectric point of silica. The isoelectric points (IEPs) of  $Q^1$  and  $Q^2$  are around a pH value of 3.0.<sup>20</sup> However, the IEP of  $Q^3$  sites is at around pH = 2. The absolute value of the IEP of a silica gel differs due to the type of silica precursor (e.g., quaternary and/or ternary monomer), Q/T site concentrations, existence of other components (e.g., drug), temperature, and so forth. Nevertheless, the charge matching regime can be assumed to lie within the pH value range from 1.5 to 3.5. On the other hand, the amount of water can also modify the kinetics of drug release. At very acidic conditions, a substantial fraction of water can be tied up in hydration of the acid and protonated drug as a hydration shell of  $H_3O^+$ ,  $Cl^-$ , and  $D^+$ . Larger pores and faster release times are observed for TEOS gels prepared at weakly acidic pH values,

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**Figure 8.** SEM micrographs of aromatic substituted spray dried gels before and after (w) drug dissolution.



**Figure 9.** pH ranges in which different charge scenarios exist.

whereas slower drug release kinetics are found at charge matching pH values.

Covalent bonding of the organic moieties to the inorganic framework imparts hydrophobicity/hydrophilicity to the silica gel depending on the choice of organic substitution in the monomer precursors. Different hydrophobic precursors (ETS, PhTS, and DPhDS) have been used in this study. Phase separations have been inhibited by employing kinetically controlled faster sol–gel reactions. The reactions have been carried out at acidic pH values where a comparable hydrolysis and condensation rates of the TEOS and organoalkoxysilanes are achieved. In such hybrid gels, the Q and T sites are homogeneously distributed throughout the network, avoiding aggregation and phase separation.<sup>8</sup> Inhomogeneous distribution and crystallization of the drug molecules in the silica gels were excluded on the basis of XRD and DSC studies (not shown).

A high level of T groups in the hybrid gel leads to a decrease in the drug release. Due to the presence of alkyl/aromatic groups in the surface, the gel particles are hydrophobic and the solvent's ability to dissolve the drug molecule from the pores decreases. The superhydrophobic nature of the silica with anchored alkyl groups on the surface has been reported in the literature.<sup>21</sup>

In summary, the drug release kinetics of the evaporation induced self-assembled gels can be tailor-made by appropriate choice of organic side groups. One of the key factors enabling control over the release rate is molecular level interaction which includes noncovalent interactions such as hydrogen bonding, van der Waals forces, electrostatic forces,  $\pi$ – $\pi$  interactions, and so forth. The cooperative interactions between the guest drug molecules and the host matrix influence the diffusion of drug from the hybrid gels. The drug molecules play the role of a structure directing agent in the self-assembled silica gel system. Noncovalent interactions of Propranolol encapsulated in hybrid silica gels investigated by two-dimensional heteronuclear correlation solid state NMR spectroscopy have been reported earlier.<sup>8</sup> The study shows that there are preferential interactions between matrix T groups and aromatic naphthyl groups of Propranolol and/or SiOH groups with the polar ends of drug molecules. In addition, the porosity of the gels is clearly influenced by the presence of the drugs.

The release of PP and PS has been enhanced by the spray drying route compared to EISA gels. Generally, faster drug release was observed for SD gels. However, aromatic substituted gels show a sustained drug release. There are two main factors affecting the drug release from EISA and SD gels: the rate of removal of solvent and the size and shape of drug carrier gel particles. In the EISA method, a slow evaporation of solvent induces an assembly between drug and silica oligomer through short-range interactions. After the drying step, irregularly sized and shaped monoliths are formed from the EISA method. The drug release from the crushed monoliths is diffusion controlled whereas SD

particles often show a burst release. It has been proposed by Mathiowitz et al.<sup>22</sup> that the fast release rates of spray dried particles find applications in cases where fast drug release is needed. The release rate of PS was slower than that of PP from SD microparticles. In general, the physico-chemical properties such as size, solubility, hydrophobicity,  $pK_a$ , and amorphous nature of the pharmaceutically active substance affect the drug release behavior.

### Conclusion

Two drug molecules, Propranolol and Persantin, have been encapsulated by a sol–gel process in an organic–inorganic hybrid matrix by in situ self-assembly. In this self-assembled sol–gel synthesis, the nature of guest–host interactions and pore structures is dictated by the synthetic parameters, pH

values, and composition. The drug release increases above and below the charge matching pH regime which is centered around the isoelectric point of silica. The alkyl/aromatic substitution in the silica gels imparts hydrophobic character to the gel which controls the surface interactions of the drug as well as the diffusion barriers of the matrix. Spray drying of the self-assembled sol leads to an enhanced dissolution process. The controlled drug release achieved from the sol–gel silica systems can be further developed and applied into the large library of newly discovered drugs.

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