Non-covalent interactions of a drug molecule encapsulated in a hybrid silica gel†

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The drug molecule Propranolol has been encapsulated by a sol–gel process in an organic–inorganic hybrid matrix by *in-situ* self-assembly; the 2D HETCOR solid state NMR spectroscopy provides direct proof of the intimate spatial relationship between the host matrix and guest drug molecules.

The non-covalent *in-situ* encapsulation of a molecular species in a growing sol–gel network is a complex process.[1–3] A key question for an understanding of the imprinting properties of the included molecule is the nature and role of intermolecular surface interactions. The main difference between an ordinary physical encapsulation and a structure directing role of the guest molecule on the matrix genesis critically depends on the strengths, selectivities and cooperativities of non-covalent guest–host interactions.

As an example of such host–guest systems, the inclusion of a pharmaceutical drug molecule, Persantin, in a hybrid silica sol–gel system has been recently suggested as a novel means for the fabrication of controlled release systems.[4] Such hybrid sol–gel materials were synthesized from a mixture of precursors,‡ *i.e.* a quaternary (Q) monomer, tetraethyl orthosilicate (TEOS), and a ternary (T) monomer, for example methyl triethyl orthosilicate (MTS). The surface interactions of the drug as well as the porosity are suggested to control the release kinetics of the drug to a large extent. The genesis of such local interactions of encapsulated guest molecules during the growth of the sol–gel matrix is of general interest. The contribution of weak, non-covalent interactions can lead to a non-random local structure in an amorphous material. A possible preference for specific interaction sites can, in principle, be exploited towards a tailored design of the properties of such materials. The purpose of this study is the characterization of the local interaction between a drug molecule, Propranolol, and the host matrix of a hybrid gel from TEOS and MTS. Moreover, the question as to whether the final sol–gel product is a genuine hybrid material rather than a composite of domains which are rich in Q and T building groups is investigated.

Fig. 1 shows the release of Propranolol from three hybrid gels and the release kinetics is clearly slower with a higher coverage of methyl groups in the hybrid material. The methyl groups of MTS are not hydrolyzed and are implemented for surface modification of the host material. An analysis of the kinetic release properties[5] indicates that the release of the drug is mainly diffusion controlled for all compositions. The molecular structure of Propranolol (Fig. 1) offers a variety of functional groups for intermolecular interactions that can direct the structure formation and self-assembly in a sol–gel process. At the low synthesis pH value of 2.2 applied in this study, the molecule is protonated at the amine function. Therefore, the surface charge of the silica matrix is close to the isoelectric point. The release kinetics assumes a minimum in this pH range which is suggested to be a result of optimised charge matching between protonated drug and the moderately negative gel surface.[4] The release kinetics is also determined by the formation of non-covalent interactions, as can be concluded from Fig. 1 for a series of gel materials with different compositions. The drug molecule cation carries two hydrogen-bond donor functionalities which can interact with the silica host framework: the protonated amine and the alcohol group attached to C5. Other interactions can be formed based on van der Waals interactions between the methyl groups of MTS and the methyl groups of the drug (C1 and C2), or the aromatic naphthyl unit. The molecule can be regarded as having a polar end with the protonated amine and a nonpolar end with the aromatic system. The competition and/or cooperativity of such weak, non-covalent interactions are of fundamental interest for an understanding of the generation and properties of such hybrid systems.

These questions are probed by employing multi-nuclear heteronuclear correlation (HETCOR) solid state NMR spectroscopy.[6] The HETCOR technique probes the heteronuclear dipolar interaction, whose strength decreases with increasing internuclear distance. Signals in the two-dimensional spectrum appear only when both nuclei are close to one another on a local scale (up to $\sim$ 1 nm). However, ^{1}H chemical shifts in systems which are rich in

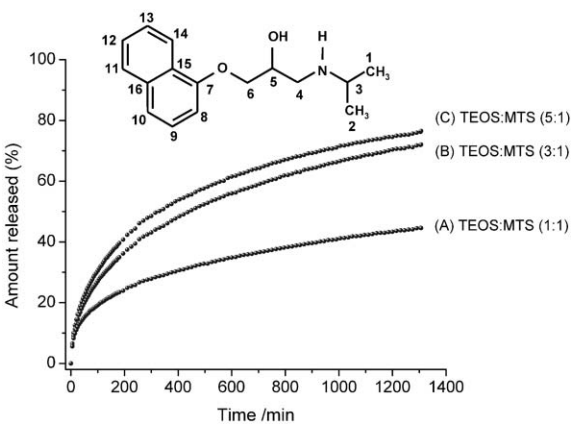

Fig. 1 Molecular structure and release kinetics of Propranolol from hybrid gels prepared at pH = 2.2.

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hydrogen bonds are notoriously difficult to interpret. The proton shielding in hydrogen bonds depends to a large extent on the hydrogen bond strength which is hard to predict *a priori* in such amorphous hybrid materials. Therefore, we have applied the HETCOR technique in a combined strategy to generate a link between three connectivity partners. ^{29}Si–^{1}H heteronuclear correlation is applied to map the local neighbourhoods between all silicon sites and all proton species in the material. This leads to a chemical shift assignment of protons which are associated with Q and T sites, *i.e.* silanol protons and locally adsorbed water. In addition, ^{13}C–^{1}H heteronuclear correlation allows one to separate OH protons from organic groups in the drug molecule and the methyl groups in T sites. Both proton correlations are then combined to derive an indirect correlation between carbon and silicon. Fig. 2 shows the ^{13}C–^{1}H and ^{29}Si–^{1}H HETCOR data of the sample with a TEOS : MTS ratio of 3 : 1. Spectral peak assignments are derived from the expected self-correlations of species in the system. For example, a group of peaks in the two-dimensional ^{13}C–^{1}H HETCOR spectrum is assigned to the correlations between protons and carbons in the aromatic group of the drug, and these are located in the box labelled as 'A' in the Figure.

Similarly, the methyl groups of the drug, B, and the MTS groups, C, are clearly observed. These groups exhibit further intermolecular correlations. The ^{13}C peaks of the side chain, C3–C6, of the drug only show the self-correlation peaks and the corresponding spectral range is therefore omitted for clarity. The ^{29}Si–^{1}H HETCOR data also contain self-correlation peaks for the T groups (D) and a range of cross peaks for the silanol protons and Q^3/Q^2 groups, labelled E.

The proton chemical shifts of Q^n or T^n for $n < 4$ (Q) or $n < 3$ (T) between 2 and 7 ppm are assigned to hydrogen-bonded SiOH and/or H_2O at the surface of the hybrid gel. The correlation between Q^4 ($\delta_{Si} \sim -110$ ppm) and these silanol protons is very weak, as expected. However, the Q^4 sites show a clear correlation with the methyl protons of the MTS groups ($\delta_{Si} \sim -110$ ppm/$\delta_H \sim 0.4$ ppm). These methyl protons also show a HETCOR signal with Q^3 and Q^2 groups, and the entire Q–T correlation pattern is shown in the box labelled Q/T. This observation is a clear proof of the close proximity between Q and T groups and thus the hybrid nature of the material. The second box labelled Q/T ($\delta_{Si} = -50$ to -65 ppm/$\delta_H = 2$ to 6.5 ppm) shows the correlation of the T groups with the SiOH–H_2O which may originate from silanol groups in T units, but can also show a neighbourhood to Q units. The weak correlation with silanol groups is especially interesting for the T^3 sites which do not have their own silanol function.

The boxes in Fig. 2 which are labelled with numbers assign the cross peaks for surface interactions of the drug molecule. Such correlations provide unambiguous information on the interactions that may determine the drug stability and leaching properties from the material. Box 1 shows clear evidence of the interaction of the methyl groups (^{1}H dimension) of the T units with the aromatic ring system (^{13}C dimension) of the drug. Further information can be extracted from boxes 1′ and 1″. While 1″ can be simply assigned to the $^{1}H_{aromatic}$–$^{13}C_T$ interaction, the box 1′ indicates that these protons are in a very special magnetic environment. We believe that the extension into the negative chemical shift range is a consequence of a negative ring current effect of these protons above the plane of the π system of the drug, but not all correlated methyl protons seem to show this effect. These observations indicate that the matrix methyl groups show an interaction with the aromatic π system with unspecific orientations. These peaks, 1, 1′ and 1″, also appear as the only intermolecular correlations at a shorter contact time of 0.8 ms (see ESI†) which proves that this interaction is of significant relevance, and it eventually indicates the existence and the controlling factor for the structured self-assembly process of the hybrid system.

The centre of gravity of the cross peak in box 2 coincides in the ^{1}H dimension with the hydrogen-bonded SiOH groups which are

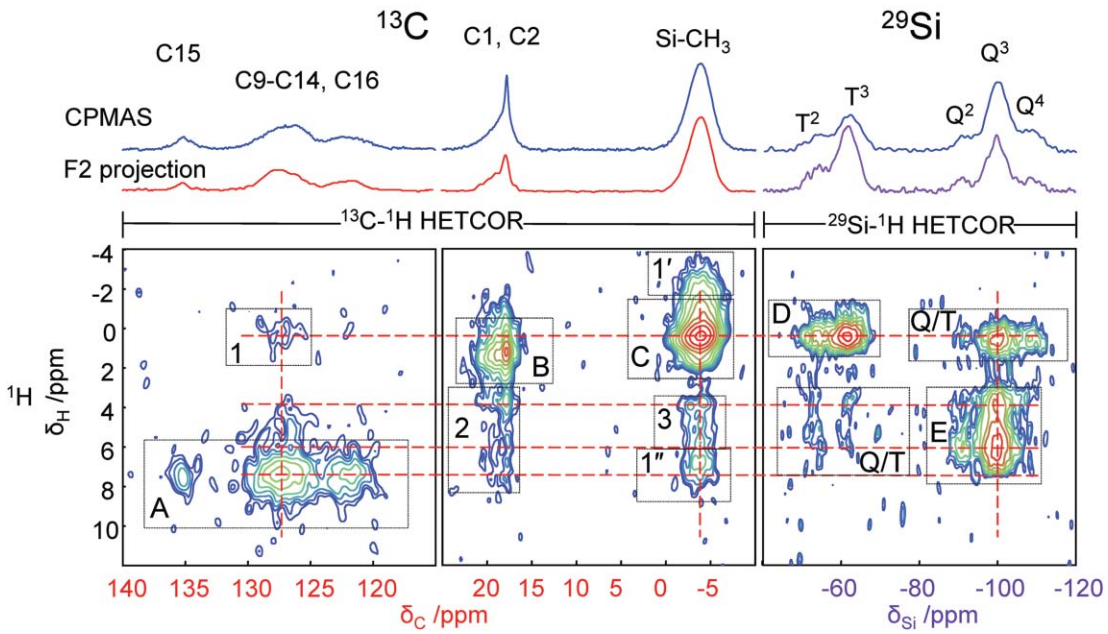

Fig. 2 The 2D ^{13}C–^{1}H and ^{29}Si–^{1}H FSLG HETCOR NMR spectra of hybrid gel at MAS of 12.5 kHz. A contact time of 1 and 2 ms was used for the ^{13}C–^{1}H and ^{29}Si–^{1}H experiments, respectively.

of the same origin as the self-correlation peak in box E. These protons correlate with the ^{13}C signal of the methyl carbons of the drug. The signal in box 3 is most likely a correlation between the matrix T groups and weakly hydrogen bonded SiOH or H_2O.

The HETCOR data provide ample evidence for the intermolecular correlation between the matrix T groups and the aromatic naphthyl unit of the drug. Additionally, the HETCOR data indicate that the C1, C2 methyl groups of Propranolol and the Q^3 units in the matrix are close neighbours. Although an interaction between the aromatic fragment and SiOH is not completely excluded, the HETCOR data show clearly that the hydrophobic part of the drug molecule associates preferentially with the hydrophobic part of the matrix. Secondly, but less selectively, the polar end of the drug interacts with the hydrophilic SiOH groups. An optimized encapsulation will be formed, when both interactions are possible for the same drug molecule. This conclusion is in good agreement with the sustained release upon increasing the T group content in the hybrid gel matrix (Fig. 1). The HETCOR method is well suited to investigate these interactions and help to understand self-assembly in amorphous systems.

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Notes and references

‡ Synthesis. In a typical synthesis of (1 : 1) hybrid gel, Propranolol, PP, (0.44 g) was dissolved in a mixture of water (4.5 ml) and ethanol (5.8 ml). To this solution a mixture of TEOS (5.7 ml) and MTS (5.1 ml) was added. The solution was stirred while adding 1.0 M HCl (0.1 ml). 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. The other stoichiometric compositions were adjusted, so that the Si : PP content was constant (Table S1 in ESI†). The polymerized hybrid silica gels were dried at 323 K to constant weight. All gels were treated in a ball mill for 3 min at 200 rpm to obtain a similar particle size distribution.

Release kinetic test. All release kinetic tests were performed at 310 K and 100 rpm under sink conditions in a VK 7010 dissolution bath with an auto sampler (VanKel industries, NJ, USA), and 900 ml of double-distilled water was used as the release medium. The gel samples were packed in a gelatine capsule and approximately 50 mg drug were present per capsule. The drug concentration in the release medium was measured by UV/VIS spectrometry at 289 nm for Propranolol hydrochloride.

Solid state NMR. The 2D spectra were acquired on a Bruker ultrashield 500 Avance II^+ spectrometer and a wide bore 11.7 Tesla magnet with operational frequencies for ^1H, ^{29}Si and ^{13}C of 500.12, 99.36 and 125.77 MHz, respectively. A 4 mm double resonance probe with magic angle spinning rate of 12.5 kHz was employed in all the experiments. The sample was packed in a ZrO_2 HRMAS rotor and the volume was restricted to the middle of the rotor. The ^{29}Si–^1H FSLG HETCOR experiments were recorded with 72 scans, 80 rows and a CP contact time of 2 ms, while in ^{13}C–^1H HETCOR, 400 scans, 76 rows and a 1 ms contact time were used. Further experimental details and parameters for the 2D ^{29}Si–^1H FSLG HETCOR and ^{13}C–^1H FSLG HETCOR NMR are given in Table S2 in ESI.†

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