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CHEMIADSORBATES OF DRUGS ON SILICA: A NEW APPROACH TO DRUG RELEASE MODIFICATION

Ch. Eckert-Lill, N. A. Lill, W. Endres and H. Rupprecht

Department of Pharmaceutical Technology
University of Regensburg
Universitätsstr. 31
D-8400 Regensburg, FRG

ABSTRACT

The preparation, characterization and in-vitro release of 2-phenylethylalcohol and thymol chemiadsorbates on a porous silica support of mean pore size of 10 nm are described. Drug molecules are linked to the silica surface by ≡Si-O-C≡ bonds via their alcoholic or their phenolic group, respectively. UV and IR spectroscopy were used to identify the chemiadsorbates and to characterize the adsorbed state of the drug molecules. The in-vitro release of the active component from this type of immobilized drug was found to be dependent on drug structure, the preparation technique (surface coverage of the chemiadsorbate) and the pH of the dissolution fluid. In the latter case increasing rates of release occured by increasing the pH. The release profiles are discussed here, considering the possible use of these chemiadsorbates in drug release modification.

INTRODUCTION

Drug molecules with reactive functional groups such as alcoholic or phenolic OH-groups can be chemically linked to silica surfaces by ≡Si-O-C≡ bonds

[1,2]. In this chemiadsorbed state they form a new type of prodrug, an immobilized drug on colloidal or porous silica supports. In contact with aqueous dissolution fluids the ≡Si–O–C≡ bonds are hydrolyzed, releasing the drug molecules as alcohol or phenol into solution.

In this paper the preparation and characterization of 2–phenylethylalcohol and thymol chemiadsorbates on a porous silica support are described and the in–vitro release of the chemiadsorbed drugs in aqueous solution in the pH range 2 – 8 evaluated.

MATERIALS

Silica supports:

KG 100:

porous silica, d_{pore} = 10 nm; spec. surf. area (BET, N_2) = 300 $m^2 \cdot g^{-1}$ [3]; particle size = 200 - 500 μm (E. Merck, Darmstadt, FRG)

Aerosil 200 (A200):

Nonporous, fumed silica; spec. surf. area (BET, N_2) = 210 $m^2 \cdot g^{-1}$ [4]; primary particle size = 12 nm
(Degussa, Frankfurt a. Main, FRG)

Chemicals:

Thymol, 2–phenylethylalcohol, pyridine, cyclohexane, 1,2–dichloroethane, benzene, chloroform, and methanol were all of analytical grade (E. Merck, Darmstadt, FRG)

METHODS

Preparation of the silica–drug–chemiadsorbates

a. Activation of the silica surface by chlorination

Dry silica was reacted under careful exclusion of moisture with thionyl chloride in benzene suspension: 600 ml thionylchloride/benzene (molar ratio 1:4); 50 g KG 100; reaction conditions = 363 K, 60 h.

The chlorinated silica was purified for 3 h under vacuum at room temperature, followed by 473 K, 8 h, p = $8 \cdot 10^{-3}$ Pa.

b. Chemiadsorption of drug

The chlorinated silica was suspended in carefully dried drug solutions (solvents: chloroform + pyridine; cyclohexane + pyridine) or in a surplus of the liquid drug + pyridine. Quantities and individual reaction conditions are given in TAB. 1.

c. Purification of the chemiadsorbates

Volatile substances were removed by heating in vacuo
T_{max} = 373 K, time = 8 h, p = $8 \cdot 10^{-3}$ Pa;
Additional leaching with dry methanol was also applied.

Quantitative measurement of chemiadsorbate drug content:

This was achieved by total hydrolysis of the drug by leaching 50 – 200 mg chemiadsorbate with phosphate buffer, 50 ml, pH 7.4 at 310 K, 24 h, with subsequent UV monitoring of the drug in the supernatant. Drug content of the chemiadsorbates was independently confirmed by C–elemental analysis (Central Analytical Department, Faculty of Chemistry and Pharmacy, University of Regensburg).

UV–Spectroscopy

Spectrophotometer DMR 10 (Zeiss, Oberkochen, FRG) with quartz cells (0.1–1 cm) for spectra recording.

a. Chemiadsorbates:

150 mg micronized chemiadsorbate + 100 mg Aerosil 200 (as suspension stabilizing agent) were dispersed in 5 ml cyclohexane by ultrasonification: 10 min.; Sonorex RK 106 (Brandlin, Berlin, FRG)

b. Physiadsorbates:

Preparation *in situ*: Aerosil 200, 150 mg, dried at 423 K, 16 h, dispersed in appropriate drug solutions by ultrasonification

c. Drug release monitoring:

Shimadzu double beam spectrophotometer UV 210 (Kontron, Munich, FRG), with flow cell (1 cm), connected with a paddle apparatus (USP XXII).
500 ml dissolution fluid, 410 K, 50 r.p.m., pH adjusted by HCl and phosphate citrate buffer); adsorbate 0.05 – 1.5 g

IR–Spectroscopy

Spectrophotometer 580 (PERKIN ELMER, Überlingen, FRG) with Interdata computer 6/16 (Munich, FRG), software SPECT 580 with programmes for spectra subtraction and compensation;

TABLE 1

Thymol and 2-Phenylethylalcohol-Chemiadsorbates on Porous Silica

Product Code	Reaction conditions	Surface coverage	
		$\mu mol \cdot m^{-2}$ [1]	$mg \cdot g^{-1}$ [2]
TH1	Thymol : 75 g Adsorbent : Chlorinated silica, 23 g Solvent : Chloroforme (100 ml) with pyridine (160 ml) Temp. : 60° C Time : 4 h	0.05	0.021
TH2	Thymol : 11 g Adsorbent : Chlorinated silica, 18 g Solvent : Cyclohexane (100 ml) with pyridine (10 ml) Temp. : 80° C Time : 20 h	2.11	0.095
PE8	Phenylethyl-alcohol : 2.37 g Adsorbent : Silica, 14 g Solvent : Cyclohexane (100 ml) Temp. : 80° C Time : 4 h	0.53	0.013
PE4	Phenylethyl-alcohol : 550 g Adsorbent : Chlorinated silica, 38 g Silica dispersion in phenylethylalcohol with pyridine (150 ml) Temp. : 80° C Time : 4 h	3.75	0.119

[1] obtained by total hydrolysis
[2] drug content of the adsorbate

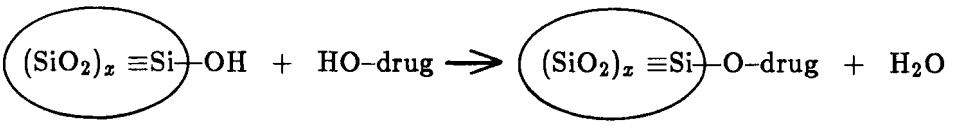
IR cell with integrated heating device (max. 900 K), CaF_2 windows, connected with a vacuum pump system (E2M5, Edwards, Frankfurt a. Main + TPH 110, Pfeiffer, Wetzlar, FRG) for self supporting (chemiadsorbate) discs.

IR liquid cell (PERKIN ELMER, Überlingen, FRG) with CaF_2 windows for drug solutions.

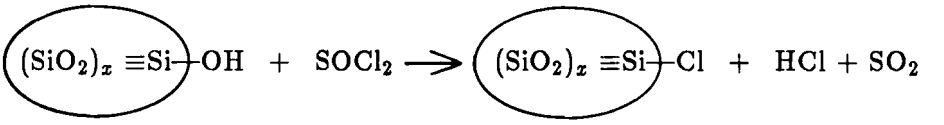
RESULTS AND DISCUSSION

Chemiadsorption at the silica surface

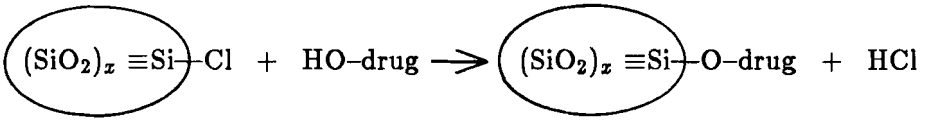
Silanol groups are located on the surface of silica, which can react with the hydroxyl groups of alcohols or phenols by condensation, according to:



Thus, ≡Si–O–C≡ bonds are formed and water is cleaved off. For this surface reaction temperatures > 450 K are necessary to obtain a reasonable yield of chemiadsorbed species [1]. Another route of reaction was preferred throughout this study in order to avoid possible degradation of drug molecules at these relatively high temperatures [5]. In a first reaction step the silica surface was activated by reacting the surface silanol groups with thionyl chloride:



In this way ≡Si–Cl groups are introduced onto the silica surface. The bond is to a great extent ionic in character due to the differences in electronegativity between the silicon and the chlorine atoms. Therefore this bond reacts easily with nucleophilic agents, which attack the silicon atom [6]. As a result the surface ≡Si–Cl groups react vigorously with water and with alcohols and phenols, forming ≡Si–O–C≡ links between the silica and the drug molecules:



During this *second step*, the reaction of chlorinated silica with the phenol or the alcohol or corresponding solutions (cyclohexane as solvent), temperatures in the range 330 – 360 K are sufficient to link the drug chemically to the silica support. Pyridine was added to the reaction mixtures as a catalyst, activating the alcoholic OH groups of 2–phenylethylalcohol and simultaneously capturing the HCl generated during the surface reaction [7]. The results of the chemiadsorption procedures are summarized in TAB. 1.

Characterization of the adsorbed state

Differentiation between physi- and chemiadsorbates:

Light absorption of the adsorbed drug molecules on the silica support was analyzed in the UV and the IR range, both of physi- and chemiadsorbates and compared with the pure drug. Most of the characteristics shown by spectra of the pure drug are also exhibited by the chemi- and physiadsorbate spectra. But there exist some specific differences which can be used, however, to distinguish between chemiadsorbates and physiadsorbates.

UV spectroscopy

In FIG. 1 the UV spectra of *2–phenylethylalcohol* in cyclohexane solution in the presence of 3% silica (Aerosil 200) and a chemiadsorbate suspension are contrasted. In the silica suspension an adsorption equilibrium was established, 40% of the total drug content being in the physiadsorbed state. The absorption band contour – minima and maxima – of the UV spectrum of the drug is not significantly changed by physiadsorption onto the silica surface. The (molar) absorbance, however, is reduced by 33% in the physiadsorbed state, considering the contribution to the total absorbance of both the free and the adsorbed 2–phenylethylalcohol in the silica suspension. This reduction in UV light interaction is however, more pronounced if the 2–phenylethylalcohol molecules are chemiadsorbed onto the silica. The molar absorbance in the chemiadsorbate is now reduced to 50% compared to the drug in solution.

The UV spectra of *thymol* show similar features (FIG. 2). In the physiadsorbed state 75% of the thymol is adsorbed at the equilibrium established in the A 200 suspension in the UV–cell – the absorption band contour of the spectrum is much the same as obtained from the pure cyclohexane solution, except for a small hypsochromic shift of the maxima (< 0.5 nm). In contrast,

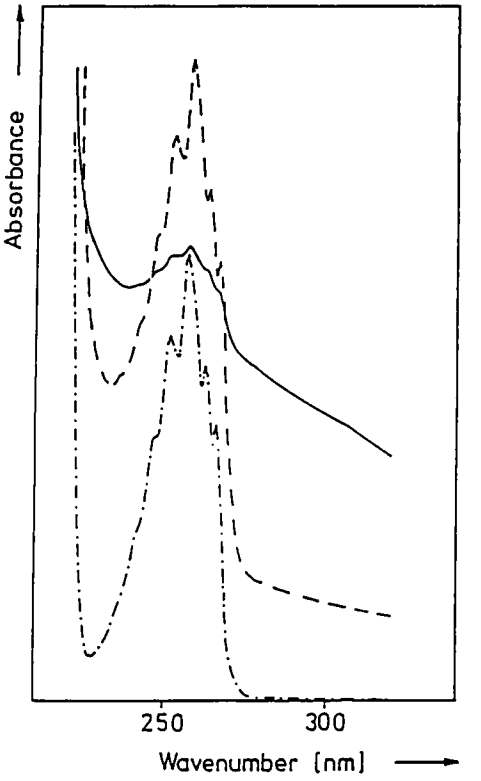


FIGURE 1

UV–Spectra of 2–Phenylethylalcohol–Adsorbates on Silica

Silica: A 200, 3%; Solvent: Cyclohexane

—·—·—·— drug solution (63.7 mmol·l^{-1})

— — — — — drug solution (63.7 mmol·l^{-1}) + silica : physiadsorbate

———— chemiadsorbate (0.8 mmol· g^{-1})

the molar absorbance is reduced to 20% in the physiadsorbates. In the chemiadsorbate spectrum this effect is much more evident. The absorbance of thymol is decreased to 10%. In addition, the chemiadsorbate spectrum of thymol on silica is characterized by band shifts of the absorption maxima at 276 and 285 nm to 270 and 276.5 nm, respectively. As a consequence, chemiadsorbates of thymol on silica can be clearly differentiated from physiadsorbates by UV–spectroscopy.

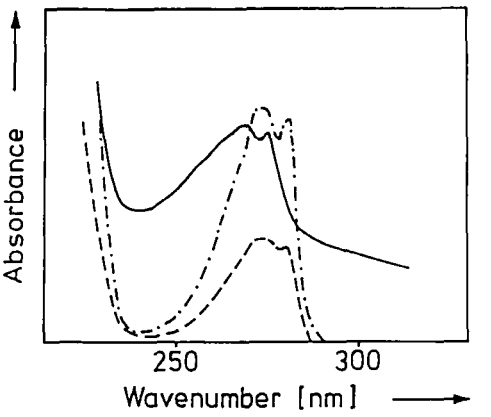


FIGURE 2

UV Spectra of Thymol–Adsorbates on Silica

Silica: A 200, 3%; Solvent: Cyclohexane

—·—·—·— drug solution (3.1 mmol·l^{-1})

— — — — drug solution (3.1 mmol·l^{-1}) + silica : physiadsorbate

———— chemiadsorbate (0.6 mmol·g^{-1})

IR-Spectroscopy

The IR spectra of the adsorbates give detailed information about the functional groups of the adsorbate and the adsorptive and their possible engagement in mutual interactions. This has been well demonstrated by Rochester for the physical adsorption of phenolic compounds on silica [8]. We wished to use IR spectroscopy as a method to identify the adsorbed species as well as to differentiate between the physi– and the chemiadsorbed state.

The IR spectra of *2-phenylethylalcohol*, the corresponding physiadsorbate and chemiadsorbate on silica are given in FIG. 3, the adsorption band assignments being listed in TAB. 2 [9,10,11].

Without giving a too detailed interpretation of the spectra (given elsewhere [12]), some essential features should be outlined in brief. Fundamental vibration bands of isolated (single) OH–groups of the alcohol and the surface silanol groups are substituted by broad adsorption bands, indicating hydrogen bonding in the adsorbates (physiadsorbate maximum at 3362 cm^{-1}, chemiadsorbate maximum at 3615 cm^{-1}).

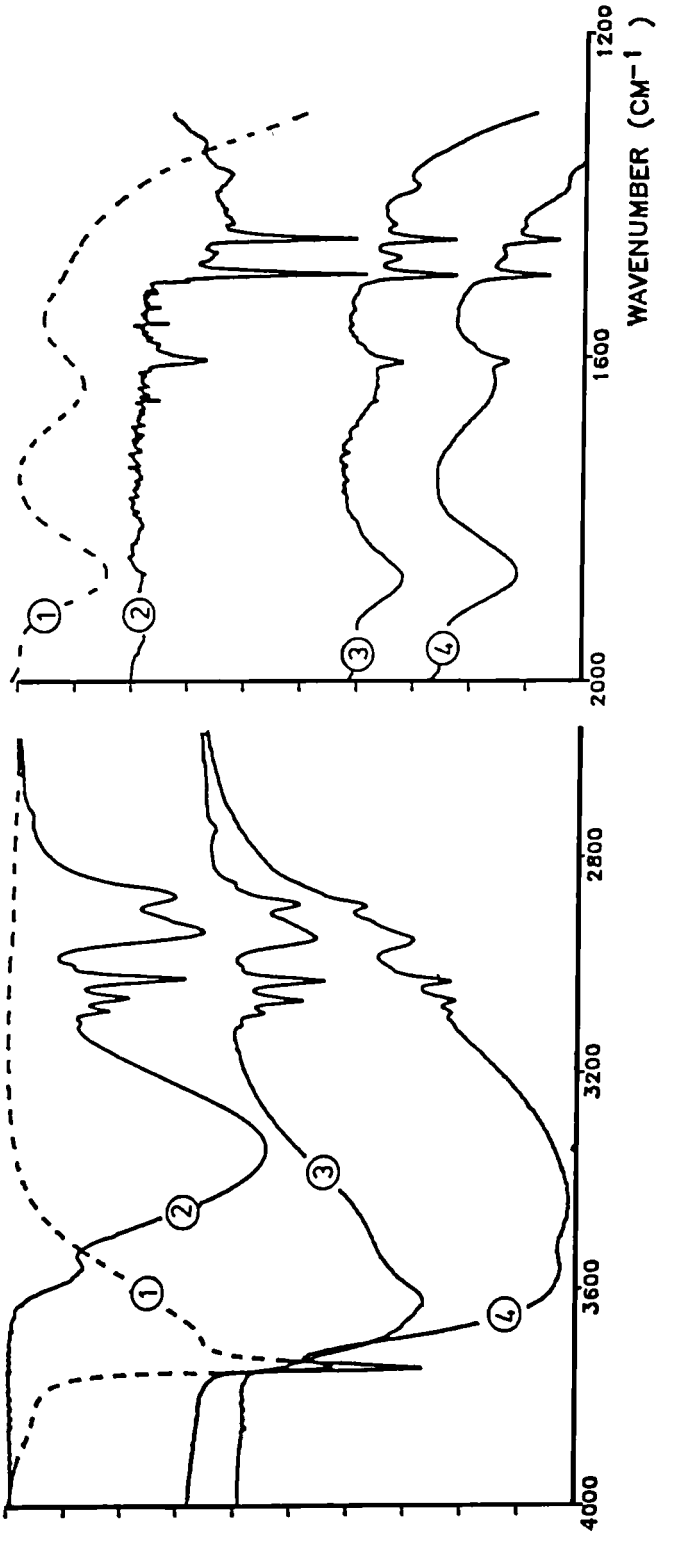


FIGURE 3

IR Spectra of 2-Phenylethylalcohol–Adsorbates on Silica

1 Silica A 200, 473 K, 2 h, p = $7 \cdot 10^{-4}$ Pa
2 2-phenylethylalcohol (thin film)
3 chemiadsorbate on KG 100; 373 K, 1 h, p = $1 \cdot 10^{-3}$ Pa
4 physiadsorbate on A 200; 300 K, p = 1 Pa

TABLE 2

IR–Absorption Bands of Silica and 2–Phenylethylalcohol in the Physiadsorbed and Chemiadsorbed State on Silica (Maxima of absorption bands given in wave numbers)

Phenylethyl–alc. liquid film	Physi–adsorbate	△	Chemi–adsorbate	△	Assignment [9,10,11]
	3748				ν SiOH on dry SiO_2
			3615		ν silanol group hydrogen bonded
3557	–		–		ν OH alcohol
	3362				ν Silanol group hydrogen bonded
3342					ν OH alcohol group hydrogen bonded
3082	3085	+3	3088	+6	ν CH arom. *20a*
3061	3064	+3	3067	+6	ν CH arom.*2*
3026	3028	+2	3031	+5	ν CH arom. *20b*
2941	2945	+3	2953	+12	ν CH asym. aliphat.
2874	2882	+8	2889	+15	ν CH sym. aliphat.
1605	1605	0	1607	+2	ν C–C arom. *8a*
(1589)					ν C–C arom. *8b*
1498	1498	0	1499	+1	ν C–C arom. *19a*
1455	1455	0	1456	+1	ν C–C arom. *19b*
1374	1386	+12	1390	+16	δ CH sym. aliphat.

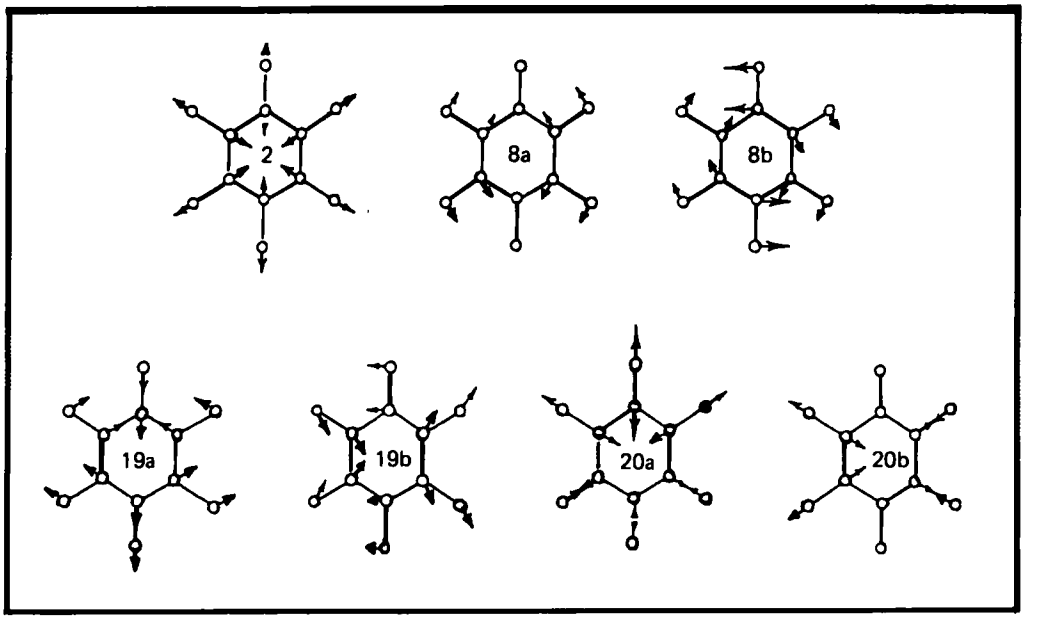


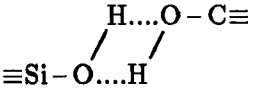
FIGURE 4

Modes of Normal Vibrations of the Aromatic Ring

Vibrations of the aromatic ring C–H and C–C groups – assigned according to the concept of Varsanyi [9] (FIG. 4) – absorb in the adsorbates at higher wave numbers. The band shifts in the physiadsorbate are on average 3 cm^{-1}, while in the chemiadsorbate spectrum larger shifts are observed, with an average of 6 cm^{-1}. This difference can be interpreted as stronger interactions between the aromatic ring system and the silica surface in the chemiadsorbate [8].

The absorption bands of the symmetric C–H fundamental stretching and deformation vibrations assigned to the aliphatic chain, are shifted to a greater extend than the aromatic C–H bands. In the chemiadsorbate blue–shifts of 15 cm^{-1} and in the physiadsorbate of 8 cm^{-1} and 12 cm^{-1} are obtained. This can be explained by a closer contact with the surface of the aliphatic group with the ≡Si–O–C≡ anchor to the silica support. The difference between physi– and chemiadsorbate may be explained on equal terms: the distance between the light absorbing groups and the silica is smaller in the chemiadsorbates, determined by the length of the ≡Si–O–C≡ group. In the physiadsorbates the anchor–group consists of a hydrogen bridge between a

surface silanol and an alcoholic OH group. As a consequence, a greater distance between the surface and the light absorbing groups may be supposed to exist in these adsorbates, as given schematically by:



Thymol is bound to the silica surface essentially by the phenolic OH–group. In the spectrum of the physiadsorbate (FIG. 5, absorption band assignment in TAB. 3) a broad and intensive absorption band between 3600 cm^{-1} and 3100 cm^{-1} indicates strong hydrogen bonds preferably established between the phenolic OH group and the surface silanol groups of the silica. There may be also some contribution to this band by hydrogen bonds between the π–electron system of the ring and surface silanols [8], mutually interacting silanol groups, and strongly adsorbed water molecules [2].

In the chemiadsorbate spectrum the band assigned to hydrogen bonds is accordingly weaker, indicating the interactions mentioned above.
The ≡Si–O–C≡ bond itself cannot be detected in the spectrum; the corresponding absorption band is superimposed by the very strong lattice absorption of the SiO_2–matrix.

The signals of the aliphatic entities (methyl and isopropyl groups) of the thymol molecule, i.e. the symmetric and asymmetric fundamental vibration bands of C–H, remain unaffected or are only slighty shifted in the physiadsorbate ($\leq \triangle$ 3 cm^{-1}). The band assigned to vibrations of aromatic C–H (ν C–H *20b*, see FIG. 4), has been shifted by 5 cm^{-1} to higher absorption energies.

In the chemiadsorbate stronger interactions between the aromatic ring and the silica surface obviously influence IR light absorption. Hypso– and bathochromic shifts of corresponding absorption bands are now observed. The band at 1518 cm^{-1}, assigned to C–C aromatic bonds (*19b*, see FIG. 4) has probably been shifted to 1509 cm^{-1}, where an intensive band is seen in the spectrum.

As a result, the UV and IR spectra of drug–silica adsorbates can be reliably used to identify organic species at the surface. In addition, they give information about the interactions in the adsorbates themselves. Conclusions can thus be drawn concerning the adsorbed state (physiadsorption – chemiadsorption) and the consequences for drug release and stability of the adsorbates.

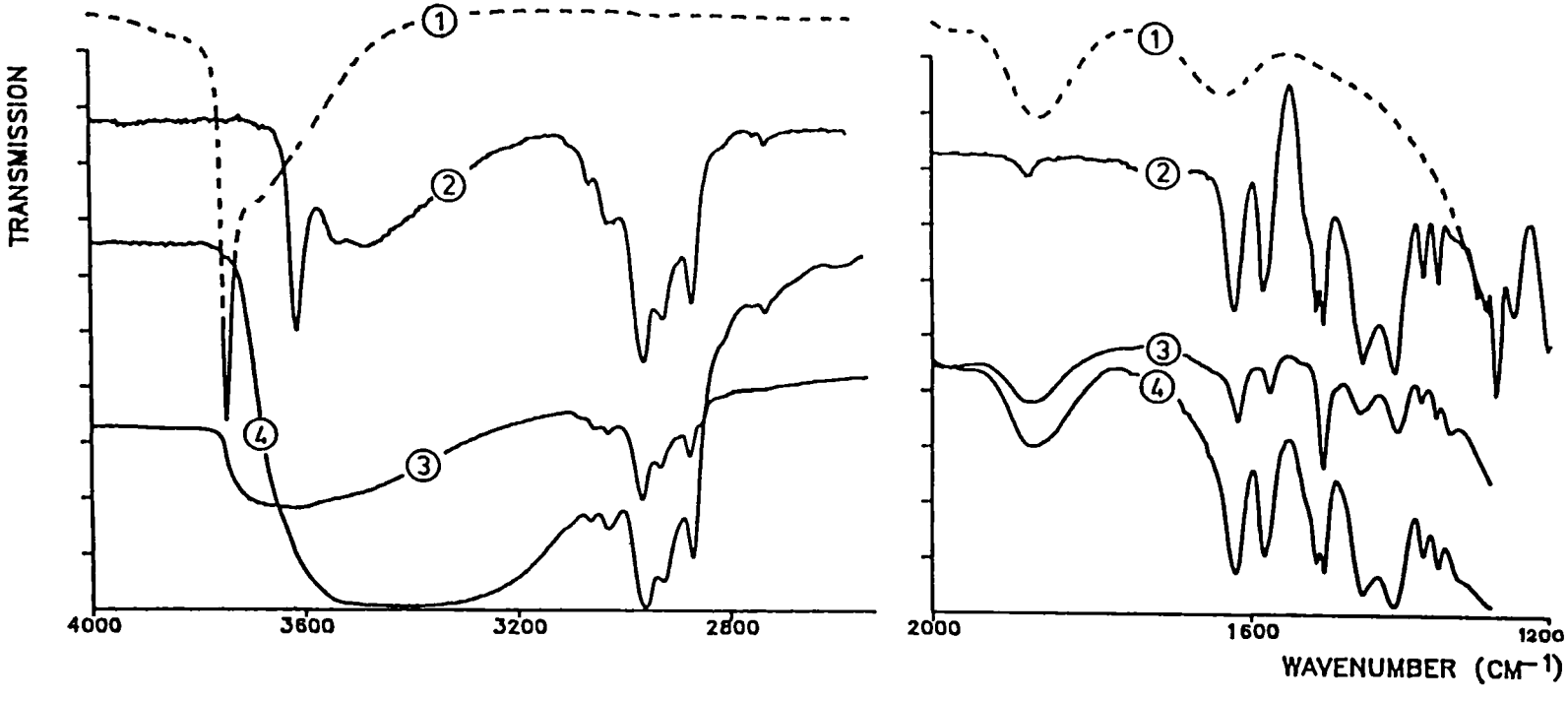


FIGURE 5

IR–Spectra of Thymol–Adsorbates on Silica

1 Silica A 200; 473 K, 2 h, p = $7 \cdot 10^{-4}$ Pa
2 thymol solution, 0.3 mmol·l−1 in CCl_4 (solvent spectrum compensated)
3 chemiadsorbate on KG 100; 373 K, 1 h, p = $1 \cdot 10^{-3}$ Pa
4 physiadsorbate on A 200; 293 K, $1 \cdot 10^{5}$ Pa

TABLE 3

IR–Absorption Bands of Thymol in the Physiadsorbed and Chemiadsorbed State on Silica
(Maxima of absorption bands given in wave numbers)

Solution in CCl_4	Physi–adsorbate	△	Chemi–adsorbate	△	Assignment [9,10,11]
3613	–		–		–OH (phenol)
3481	–		–		–OH...O–
–	broad band ≈3650–3400		broad band ≈3650–3400		hydrogen bonds of silanol– and phenolic OH–groups
3061	3064	3	3052	9	ν C–H arom. *2*
3025	3030	5	3029	4	ν C–H arom. *20b*
2962	2961	1	2965	3	ν C–H asym. aliphat.
2925	2928	3	2932	7	ν C–H aliphat.
2870	2870	0	2876	6	ν C–H sym. aliphat.
1621	1620	1	1618	3	ν C–C arom. *8b*
1581	1584	3	1578	3	ν C–C arom. *8a*
1518	1518	0	–	–	ν C–C arom. *19b*
1419	1421	2	1417	2	ν C–C arom. *19a*
1509	1508	1	1509	0	– ? –
1460	1460	0	1464	4	δ C–H asym. aliphat.
1383	1384	1	1386	3	δ C–H sym. aliphat.
1364	1365	1	1367	3	δ C–H aliphat.

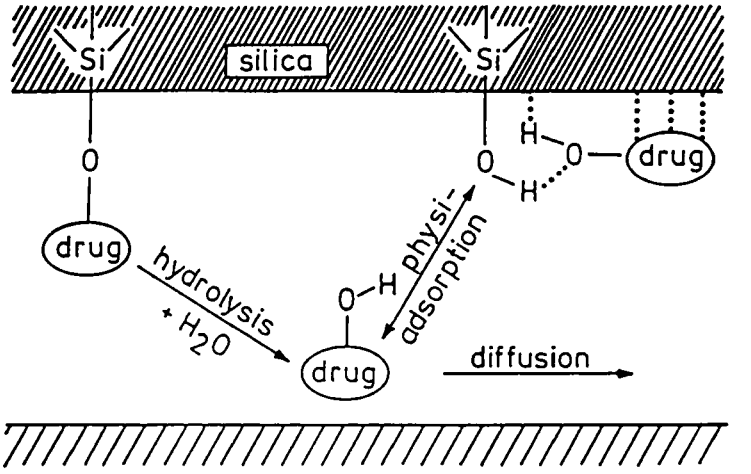


FIGURE 6

Schematic Illustration of Drug Release after Contact of a Drug Chemiadsorbate on Porous Silica with Water

In vitro drug release

The release from drug chemiadsorbates on porous silica supports in aqueous dissolution fluids depends on several processes. Firstly, *cleavage* of the surface bond, followed by possible physical adsorption and the establishment of an *adsorption equilibrium* between free (dissolved) and *physically adsorbed* species. Finally, *transport* of the free drug molecules out of the porous matrix by *diffusion.* This is schematically given in FIG. 6.

The ≡Si–O–C≡ linkage between the silica surface and the drug molecules exhibits a great tendency to undergo hydrolytic cleavage as a result of the differences in electronegativity between the silicon and the oxygen atom [6]. Therefore the chemiadsorbed molecules are set free by hydrolysis after contact of the chemiadsorbate with an aqueous dissolution fluid, releasing the orginal alcohol or phenol:

$$(SiO_2)_x \equiv Si\text{–}O\text{–drug} + H_2O \rightarrow (SiO_2)_x \equiv Si\text{–}OH + H\text{–}O\text{–drug}$$

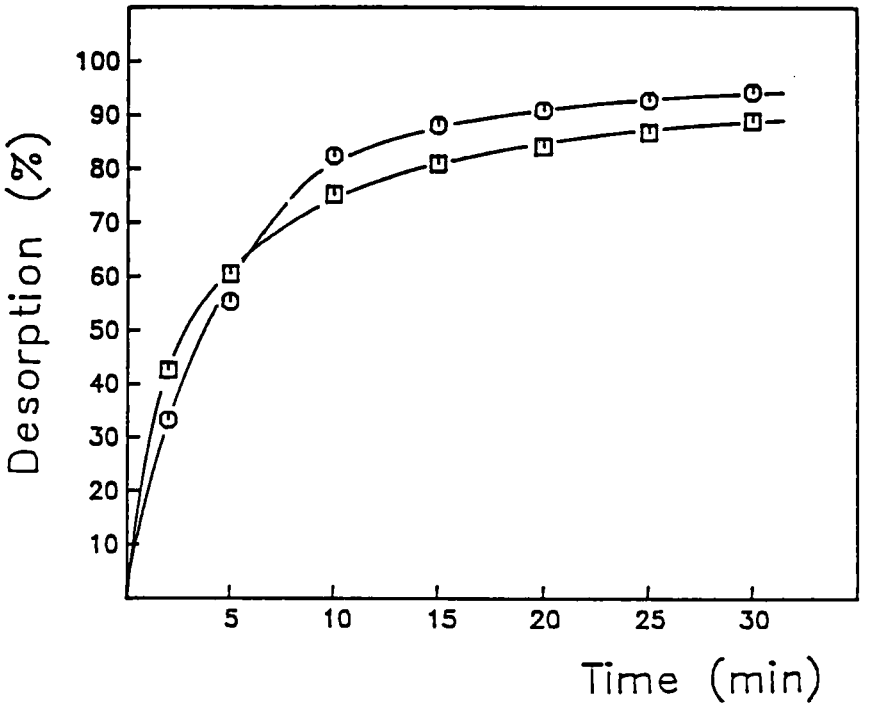


FIGURE 7

Drug Release of 2–Phenylethylalcohol from Physiadsorbates on Porous Silica

□——□ pH 2 ○——○ pH 7.4

To evaluate the specific contributions of the different mechanisms mentioned above to the release kinetics of drug chemiadsorbates the drug release from a physiadsorbate of 2–phenylethylalcohol on the same SiO_2 carrier was examined (FIG. 7). The physiadsorbate was obtained by the solvent deposition technique from a nonpolar drug solution (1,2–dichloroethane). Under the conditions of the drug dissolution test of the USP XXII, 90% of the adsorbed drug is set free within 30 min., almost independent of the pH from 2 to 7.4. The corresponding half lives of desorption were between 2 and 3 min.

This relatively rapid release from the physiadsorbates demonstrates that neither physiadsorption nor the transport out of the porous matrix have an important influence on a (possible) sustained drug release.

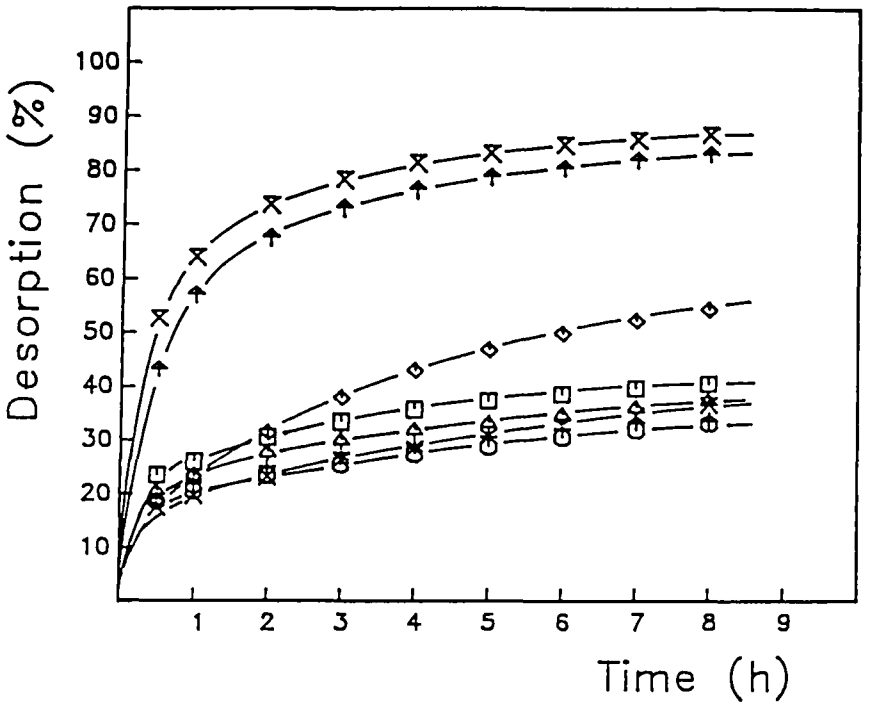


FIGURE 8

Drug Release of 2–Phenylethylalcohol from (PE4)–Chemiadsorbate with a High Surface Coverage on Porous Silica

pH 1 pH 4 pH 7.4
pH 2 pH 5 pH 8.0
pH 3 pH 6

From chemiadsorbates of 2–phenylethylalcohol (PE4) with a surface coverage of 3.72 μmol·m^{-2} the drug release depends strongly on the pH of the dissolution fluid (FIG. 8). Except for an initial phase showing a fast release, a slow drug release is observed in acidic dissolution fluids (pH 1 – pH 5) with 30–40% drug available after 8 hours. In the range between pH 5 and pH 7.4 the release rates are considerably enhanced. After 1 hour about 60% release at pH 7.4 and finally 70% release at pH 8 are observed.

The release of chemiadsorbed 2–phenylethylalcohol is also strongly dependent on the surface coverage of the chemiadsorbates as established during the preparation step.

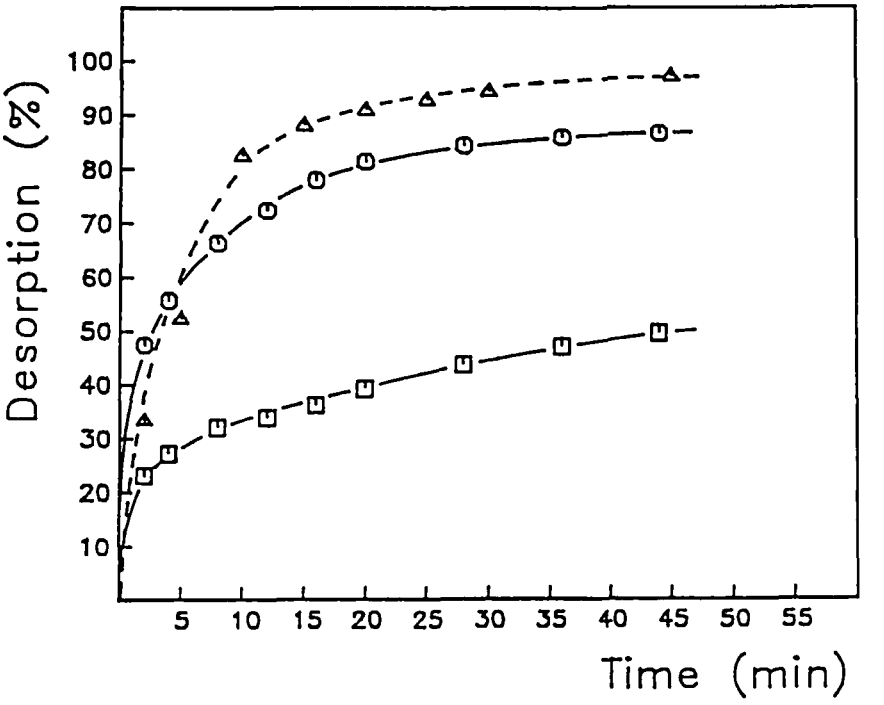


FIGURE 9

Drug Release of 2-Phenylethylalcohol from a Chemiadsorbate with a Low Surface Coverage (PE8) on Porous Silica

□——□ pH 2 ○——○ pH 7.4
▲——▲ physiadsorbate

From the chemiadsorbate PE8[3] with a surface coverage of only 0.53 $\mu mol \cdot m^{-2}$ the drug release at pH 7.4 is similar to that of the physiadsorbate (FIG. 9). This indicates that the hydrolytic cleavage is no longer the rate determining factor for the drug release under these conditions. In acidic dissolution fluids the drug release from PE8 is still controlled by the hydrolysis of the chemiadsorbate.

[3]obtained by direct reaction of pure,dried silica with the drug (TAB. 1)

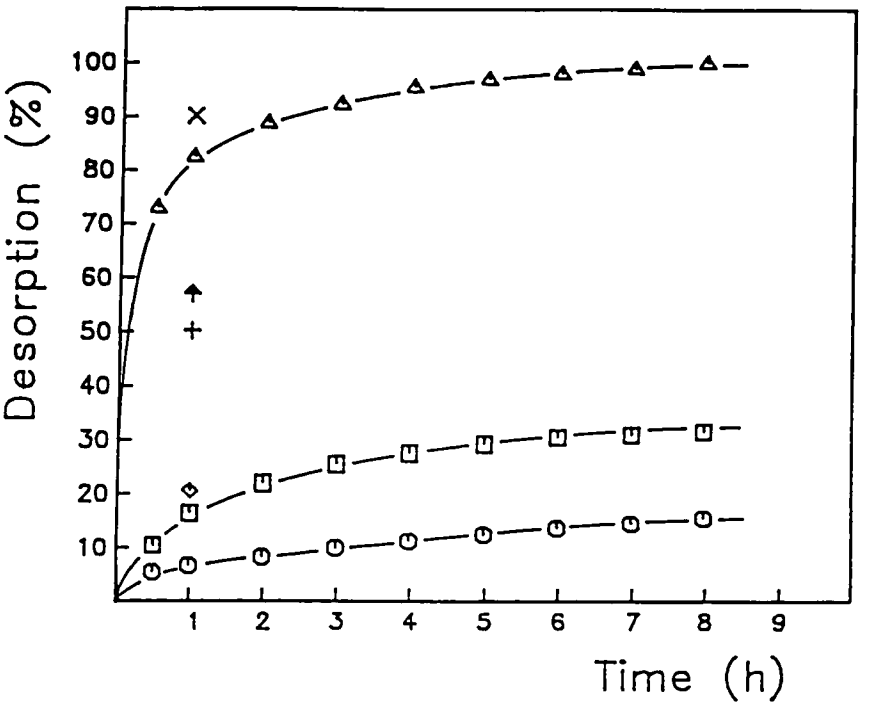


FIGURE 10

Drug Release from Thymol Chemiadsorbates with High (TH2) and Low Surface Coverage (TH1)
(Drug release of 2–phenylethylalcohol after 1 hour is given for comparison)

□——□	pH 2	(TH1)
○——○	pH 2	(TH2)
▲——▲	pH 7.4	(TH1 and TH2)
+	pH 2	(PE8)
×	pH 7.4	(PE8)
◆	pH 2	(PE4)
✦	pH 7.4	(PE4)

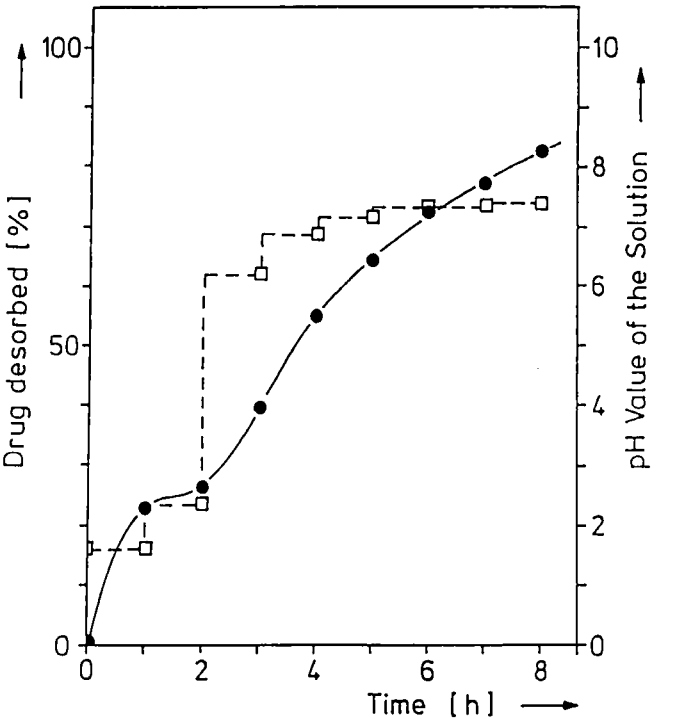


FIGURE 11

Drug Release of 2–Phenylethylalcohol from a KG 100 Chemiadsorbate (PE4) Under Half Change Test Conditions

● ——— ● 2–phenylethylalcohol
□ ——— □ pH value

Drug release from the thymol–chemiadsorbate may demonstrate, by comparison, the influence of the anchor–groups originating from an alcohol or a phenol on the rate of hydrolysis. In FIG. 10 the release pattern at pH 2 and pH 7.4 for chemiadsorbates with a different surface coverage are shown.

At pH 7.4 no significant differences in drug release rate can be observed between the different chemiadsobates of thymol TH1 and TH2. The release is also in the same range as observed with 2–phenylethylalcohol chemi– and physiadsorbates. This confirms that at higher pH the hydrolysis of these chemiadsorbate is obviously catalyzed by OH^-, becoming thereby a more rapid process.

In the acidic pH range again the chemiadsorbate with the higher surface coverage, TH2 (2.11 μmol·m^{-2}), shows slower release than TH1 with a surface coverage of 0.047 μmol·m^{-2}. In comparison with the release of 2–phenylethylalcohol, the hydrolysis of the phenolic compound is obviously a slower process. It must be considered though, that the hydrophobic substituents of thymol, i.e. the methyl– and the isopropyl–group may also hinder the attack of water molecules by an "umbrella" effect, thereby decreasing the rate of desorption.

The strong pH dependence of the hydrolytic cleavage of drug chemiadsorbates from the silica results in an almost constant release rate, provided the dissolution test is performed under the so–called half change conditions [13] (FIG. 11). Increasing rates of cleavage with an increasing pH of the dissolution fluid compensate for the typical matrix liberation effects of the porous silica support.

CONCLUDING REMARKS

The chemiadsorption of drug molecules with reactive hydroxyl groups on silica supports which is outlined in this article can be realized for a great number of alcohols and phenols with different structures (i.e. codeine, p–hydroxybenzoic acid esters) [14].

The ≡Si–O–C≡ bond between the drug molecule and the support is a silicic acid ester group and therefore easily cleaved by water. This basic reaction determines drug release and must be considered with respect to the storage stability of these chemiadsorbates. A careful exclosure of moisture seems therefore an important condition for an acceptable stability of the adsobates. Stability testing has therefore priority in our present research work.

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