*International Journal of Pharmaceutics*, 73 (1991) 221–229

*ADONIS* 0378517391002647

IJP 02458



# Chemiadsorbates of *p*-hydroxybenzoic acid methyl ester on silica as a new type of pro-drug. III. Modeling and simulation of drug release from chemiadsorbates to acid aqueous solution *

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(Received 25 January 1991)
(Accepted 10 March 1991)

*Key words*: Chemiadsorbate; Porous silica release kinetics; Non-porous silica release kinetics; Modeling; Fractal dimension; *p*-Hydroxybenzoic acid methyl ester

## Summary

The in vitro release of physi- and chemiadsorbates of *p*-hydroxybenzoic acid methyl ester (PHBAME) on a colloidal (Aerosil $0 \times 50$; BET surface 50 $m^2\ g^{-1}$) and a porous silica support (KG 100; mean pore size 10 nm, BET surface 300 $m^2\ g^{-1}$) in an acidic dissolution fluid was investigated and the release kinetics described by mathematical modeling with an analog-hybrid computer. The release from physiadsorbates on both the colloidal and the porous silica proved to be a fast process, best described by two release constants. The release from the chemiadsorbates, however, is based on different mechanisms: from the plain surface of colloidal silica (fractal dimension 2.0) the drug release can be best described by two hydrolysis reaction rates while four different reaction rates were evaluated for the release of PHBAME from the porous support. From the reaction rates and the activation energies it is concluded that the hydrolysis of the surface link between the PHBAME and the silica surface, the $\gtrless$Si–O–C$\lesseqgtr$ bond is strongly influenced by the surface character of the supports, described by their different fractal dimensions (porous support fractal dimension 2.56).

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* Dedicated to Professor Pavle Bohinc on the occasion of his 80th birthday.

## Introduction

The grafting of macromolecules with drug molecules has become of prime interest in the past years. Drugs, covalently linked to a polymer backbone offer interesting features for therapy: (1) drug targeting by the release of the drug at a

desired target tissue; (2) control of rate and amount of drug release over a desired period of time; (3) enhancement of drug bioavailability by the influence on drug solubility; and (4) stabilization of the therapeutic agent against physical and chemical deteriorating reactions (Larsen, 1989).

A second, very effective principle in drug release regulation is based on diffusion from porous matrix substances (Siegel, 1988), incorporated in tablets, capsule membranes, etc.

Stimulated by the favorable physical, chemical and pharmacological properties of silicas we selected these inorganic supports to combine the grafting of drugs onto a polymer matrix by hydrolyzable bonds with the ability of a pore system to regulate (sustain) the drug release by the diffusion processes inside the pore-framework (Unger, 1972; Rupprecht, 1983; Lee and Rupprecht, 1985; Eckert-Lill et al., 1987a,b, 1988). Compared with a great number of organic matrix substances, porous silica has an additional advantage: during the release process no swelling or dissolution processes of the matrix have to be considered in contact with physiological dissolution fluids. In previous papers (Srčič and Rupprecht, 1990, 1991) production and characterization of hydrolyzable chemiadsorbates of *p*-hydroxybenzoic acid methyl ester (PHBAME) on a porous (KG 100) and a non-porous (Aerosil $0 \times 50$) silica, respectively, were described and the desorption of the drug from both the carriers in an acidic aqueous dissolution fluid was contrasted. In this paper we describe the modeling and simulation of drug release from physi- and chemiadsorbates of PHBAME on porous and non-porous silica in an acidic aqueous dissolution fluid. From previous experiments (Eckert-Lill et al., 1987a; Srčič and Rupprecht, 1990) two main processes were evaluated responsible for the drug release from drug chemiadsorbates on porous silica carriers: firstly, hydrolysis of the drug-carrier bond at the silica surface and, secondly, the consecutive transport of the drug molecules by diffusion out of the pore structure. Due to these consecutive processes the Monte Carlo approach, usually applied to describe drug release by diffusion from porous supports (Siegel and Langer, 1986), could not be reasonably applied.

The influence of the pore structure on the drug release will be demonstrated by comparing the release from PHBAME-chemiadsorbates on the porous and the non-porous silica support. In addition, desorption experiments with PHBAME-physiadsorbates on the same carriers give an insight into the second step of the total release.

## Materials and Methods

### *Materials*

Porous silica: silica gel KG 100, $d_{pore} = 10$ nm, specific surface area (BET, $N_2$) = 300 $m^2\ g^{-1}$, particle size 200–500 $\mu$m (E. Merck, Darmstadt, Germany).

Non-porous silica: Aerosil $0 \times 50$, specific surface area (BET, $N_2$) = 50 $m^2\ g^{-1}$, mean particle size approx. 50 nm (Degussa, Frankfurt/Main, Germany).

Drug: *p*-hydroxybenzoic acid methyl ester, Pharm. Eur. II (Nipagin M) (Chemische Werke Hommel, Muellheim, Germany).

Chemicals used: analytical grade (E. Merck, Darmstadt, Germany); water: aqua purificata (Pharm. Eur.), double distilled.

### *Methods*

*Preparation of the adsorbates.* The preparation of the chemi- and physiadsorbates of PHBAME on silica was carried out as described elsewhere (Eckert-Lill, 1986; Eckert-Lill et al., 1987a,b; Lill and Rupprecht, 1989). The main features of the chemiadsorption are an activation of the silica surface by reaction with $SOCl_2$ in a first step. In this way highly reactive $\equiv Si-Cl$ groups are formed. In a second step these groups react with the hydroxyls of the drug molecules forming $\equiv Si-O-C \equiv$ groups as surface links and HCl, which is removed by heating in vacuo. Physiadsorbates (i.e., solvent deposits) were obtained by adsorption from a nonpolar solvent (cyclohexane).

*Characterization.* The adsorbates were characterized by elemental analysis, TG, DSC, UV and IR (Eckert-Lill, 1986; Lill and Rupprecht, 1989; Srčič and Rupprecht, 1991). The distinction between the physi- and chemiadsorbed state of

TABLE 1

*Surface coverage of PHBAME chemi- and physiadsorbates on porous (KG 100) and non-porous (Aerosil 0 × 50) silica and fractal dimensions of the supports*

| Carrier | Fractal dimension ($D$) | Surface coverage | | | | | |
|---|---|---|---|---|---|---|---|
| | | Chemiadsorbate load | | | | Physiadsorbate load | |
| | | Actual | | Theoretical [a] | | ($\mu$mol/m$^2$) | (mmol/g) |
| | | ($\mu$mol/m$^2$) | (mmol/g) | ($\mu$mol/m$^2$) | (mmol/g) | | |
| KG 100 | 2.56 [b] | 2.5 | 0.678 | 2.78 | 0.833 | 2.0 | 0.6 |
| Aerosil 0 × 50 | 2.00 [c] | 1.8 | 0.090 | 2.78 | 0.139 | 10.0 | 0.5 |

[a] With the supposition that the flat surface of PHBAME is about 60 Å$^2$ (from the CPK model projection).
[b] From D. Avnir, personal communication (1988).
[c] From Avnir and Farin (1983).

the adsorbates was based on IR, DSC and U.V. spectroscopy. In the IR spectrum the frequency at 1417 cm$^{-1}$ occurs only with chemiadsorbates. In the case of U.V. spectroscopy the absorption of $CH_2Cl_2$ chemiadsorbate dispersion (i.e., of supernatant after centrifugation) detected only the physiadsorbed state of PHBAME. In addition, the total drug content was quantitatively determined by U.V. spectroscopy in the supernatant liquid after total hydrolysis of the adsorbates in phosphate buffer (pH 7.4) for 24 h at 37 ° C. From both the results the exact quantity of chemically bonded PHBAME to the silica surface was determined. The purity of the chemiadsorbates, concerning physiadsorbed species, was always better than 85%. The drug content of the adsorbates, given as surface coverage, and the fractal dimensions of the silicas are listed in Table 1.

*Drug release monitoring.* Instruments: LKB Ultraspec II spectrophotometer with a quartz flow through cell ($d$ = 2 mm), connected to a paddle apparatus (USP XXII).

Dissolution fluid: 500 ml 0.01 N HCl (pH = 2), stirred at 50 rpm.

Date processing: Microcomputer Olivetti M 24 with a special software *. Each point represents an average value of at least three measurements. The standard deviation was in all cases under 5%. In the case of Aerosil 0 × 50 adsorbates approx. 3 ml samples were taken from the dissolution fluid. The colloidal carrier was then separated from the dissolution fluid by centrifugation for 30 min at 10000 rpm (Ultrazentrifuge Spinco Beckmann, rotor 75 stainless steel tubes, Munich, Germany) prior to the U.V. measurement in a quartz cell ($d$ = 1 cm).

The stability of PHBAME under the used acid condition was found to be satisfactory (Eckert-Lill, 1986).

*Analog computer simulation.* Analog-hybrid computer EAI 580 (Electronic Associates Incorporation, Westling Branch, NJ, U.S.A.) equipped with the appropriate programs (Mrhar, 1983), was used to perform simulation and modeling. The identification procedure with an adoptive model was employed for verification of the model struc-

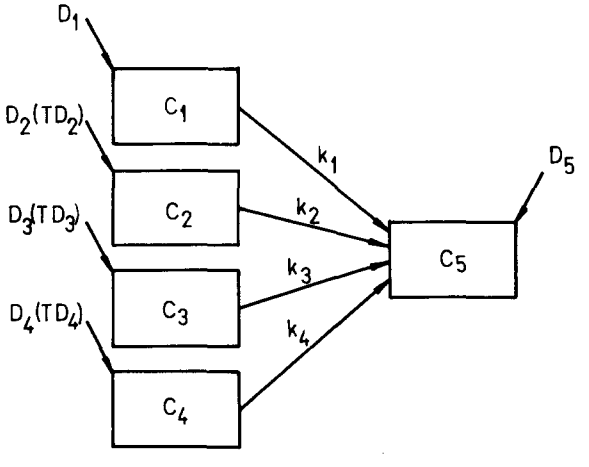


Fig. 1. Kinetic model of drug release from silica physi- and chemiadsorbates.

* Program copyright: Dr N. Lill, Frankfurt a.M., Germany.

ture. Parameters were modulated manually in order to obtain optimal accordance between the model response and in vitro drug release data, using integral square error as a criterion function (Kmetec et al., 1984).

## Model Construction for Drug Release from Chemi- and Physiadsorbates

The kinetic model to describe drug release from silica chemiadsorbates is based on the results of the hydrolysis experiments of the chemiadsorbates (Srčič and Rupprecht, 1990) and considers the additional information of the desorption kinetics from corresponding physiadsorbates (Fig. 1). As mentioned above two basic steps are assumed to determine the release from the chemiadsorbates on silica:

(a) Cleavage of the drug-carrier bond, the ≡ Si–O–C ≡ linkage, by hydrolysis after contact with water. The penetration of water into the carrier is a very fast process and, therefore, not considered in the model as a significantly rate determining parameter.

(b) Transport of the cleaved drug molecules from the surface inside of the support into the liquid bulk phase through the pores of the sup-

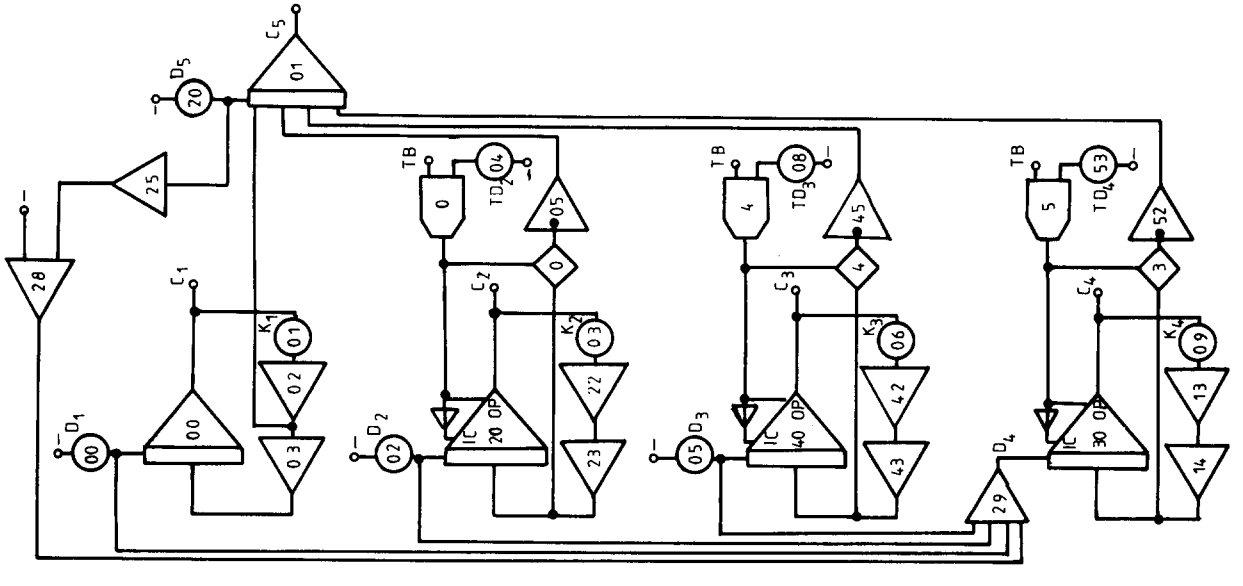


Fig. 2. Analog diagram for determination of drug release from silica physi- and chemiadsorbates. Integrators ( ) 00, 20, 40, 30 and 01 given on their outputs levels of the drug in the compartments $C_1$, $C_2$, $C_3$, $C_4$ and $C_5$, respectively. Logically controlled switches 0, 4 and 3 ( ) by comparators 0, 4 and 5 ( ) enable the integration within the optional part of time scale according to the values of $TD_2$, $TD_3$ and $TD_4$, appointed by potentiometers 04, 08 and 53 ( ). The doses $D_1$, $D_2$, $D_3$, $D_4$ and $D_5$ are introduced as initial conditions on integrators 00, 20, 40, 30 and 01 ( ) by the use of potentiometers 00, 02, 05 and 20 ( ) and by its summer 29. Parameters of the model $k_1$, $k_2$, $k_3$ and $k_4$ were introduced in potentiometers 01, 03, 06 and 09, respectively ( )

port, influenced by the pore size, pore shape, length and tortuosity. The desorption of cleaved, but still physically adsorbed drug molecules has also to be considered.

Further a priori assumptions were made:

(c) The structure of the porous silica carriers remains unaffected by the solvent due to swelling or dissolution.

(d) Important contribution of specific wall effects on drug molecules, diffusing out of the support is not expected: the mean diameter of the pores of 10 nm is more than 10 times larger than the size of a PHBAME molecule (0 = 0.85 nm, according to the CPK-model).

(e) The pH of the dissolution fluid, adjusted to 2, rules out any influence of charge effects of ionized phenolic groups of PHBAME molecules.

Compartments $C_1$–$C_4$ on Fig. 1 represent the chemi- and physiadsorbed PHBAME. In all compartments the same covalent chemical bond ≡ Si–O–C ≡ is present, but, because of different microenvironment they show different accessibility for water molecules. $D_1$–$D_4$ are 'doses' (quantity) of chemi- and physiadsorbed PHBAME in compartments $C_1$–$C_4$, and $C_5$ is the central sampling compartment (i.e., acid aqueous solution). $D_5$ is the so-called initial condition and in all cases amounted to 5%.

With $TD_2$–$TD_4$ the time delays of the corresponding hydrolysis reaction in the corresponding compartments are denoted. This uniform, concise, simplified and reduced representation was suitable for further processing by the use of computer simulation. The model was used for the drug release in both silica carriers for physi- and chemiadsorbates respectively.

In Fig. 2 the analog-diagram derived for solving the proposed mathematical model is shown.

## Results and Discussion

First of all, the release data of the physiadsorbates were processed. The simulation of the second step of the chemiadsorbate drug release clearly shows the contribution to the total rate of desorption from the chemiadsorbates. In Fig. 3 the experimental points and the simulated curve are contrasted for the release of PHBAME from a KG 100 physiadsorbate (numerical values are listed in Table 2).

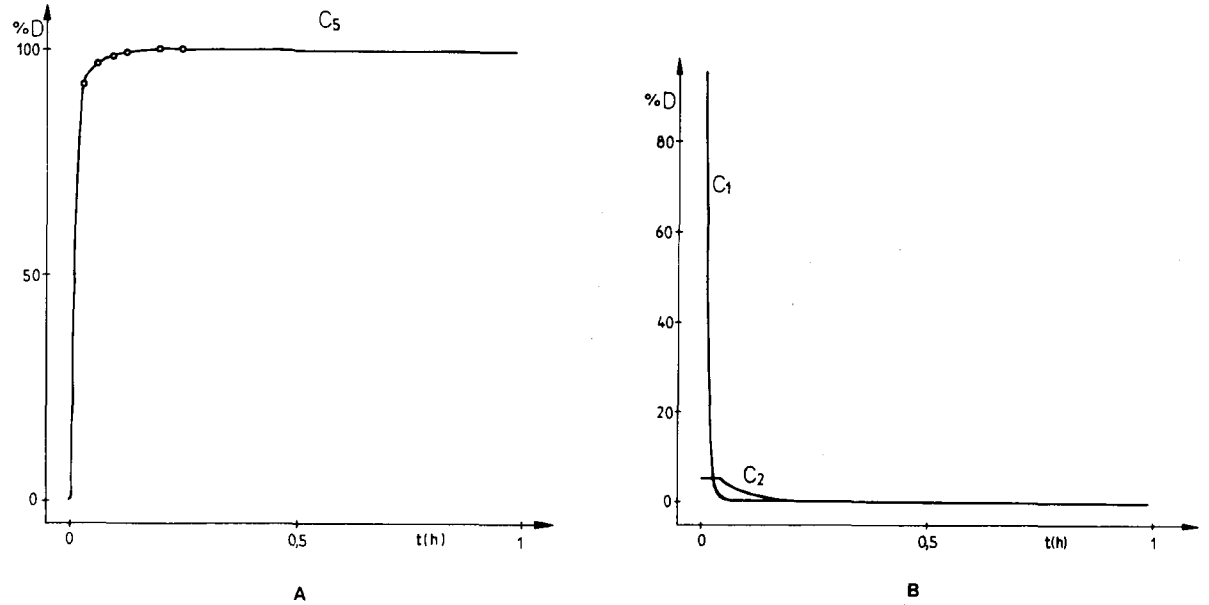


Fig. 3. Drug desorption profiles for KG 100 physiadsorbate (T = 23 °C). A. Levels in sampling compartment; ○, experimental points, curve-model response. B. Simulated levels in carrier compartments.

The desorption, even from the porous carrier, proved to be very fast and quantitative. The constant $k_1$ describes most of the drug release. About 5% of the adsorbed drug are desorbed with a short time delay characterized by $k_2$, being many times smaller than $k_1$. Probably the effect is due to the simplifying assumption of the model. A 'simple' matrix controlled release kinetics, according to the well known square root-law (Siegel and Langer, 1986), was, however, not confirmed (correlation coefficient $< 0.90$).

Eqn 1 (Siegel, 1988) describes the effective diffusion coefficient $D_{eff}$ for the drug release from the matrix:

$$D_{eff} = F \cdot D_{iw} \quad (1)$$

where $D_{iw}$ is the diffusion coefficient of the drug in aqueous solution and $F$ is a 'formation factor' considering the effects of pore geometry and topology on diffusion. Applied to a random capillary model which represents the structure of the porous KG 100, $F$ is described by:

$$F = \int_0^{\pi/2} \cos 2\theta \sin \theta \, d\theta = 0.33 \quad (2)$$

The formation factor $F$ is further connected to the tortuosity of the carrier by:

$$F = 1/\tau^2 \quad (3)$$

For the porous silica a formation factor $F = 0.39$ was calculated based on the $k_1$ constants of the desorption process from porous and non-porous carriers. This is in rather good agreement with the theoretical value of 0.33 for a random capillary model.

The slower desorption from the porous silica, compared with the release from the non-porous silica (about 2.5 times), is assigned to a structure effect of the pores. A corresponding tortuosity factor $\tau$ of 1.60 was calculated for KG 100.

Comparing the drug release data of physi- and chemiadsorbates obtained at 23 °C (Table 2), it is evident that the hydrolysis of the drug-carrier bond is the rate-determining step during the chemiadsorbate desorption from silicas. The release constant $k_1$ (comprising hydrolysis and desorption) is one order of magnitude smaller than the corresponding constant of the physiadsorbate.

In Fig. 4 the simulation of drug release from the porous KG 100 chemiadsorbate is demon-

TABLE 2

*Numerical values of drug release constants and other parameters obtained by simulation*

| | KG 100 | | | | Aerosil 0 × 50 | | |
|---|---|---|---|---|---|---|---|
| | Chemiadsorbate | | | Physiadsorbate | Chemiadsorbate | | Physiadsorbate |
| Temperature (°C): | 15 | 23 | 37 | 23 | 23 | 37 | 23 |
| k ($h^{-1}$) (releasing constant) | | | | | | | |
| $k_1$ | 8.75 | 12.5 | 36.9 | 133.0 | 41.0 | 750.0 | 334.0 |
| $k_2$ | 0.72 | 2.9 | 8.34 | 18.9 | 2.15 | 300.0 | 35.2 |
| $k_3$ | 0.11 | 0.85 | 2.63 | 0.0 | 0.0 | 6.8 | 0.0 |
| $k_4$ | 0.07 | 0.11 | 0.25 | 0.0 | 0.0 | 0.8 | 0.0 |
| D (%) (dose) | | | | | | | |
| $D_1$ | 29.0 | 29.0 | 29.0 | 95.0 | 49.0 | 49.0 | 95.0 |
| $D_2$ | 18.3 | 13.0 | 18.0 | 5.0 | 18.0 | 14.5 | 5.0 |
| $D_3$ | 12.5 | 12.5 | 12.0 | 0.0 | 28.0 | 5.0 | 0.0 |
| $D_4$ | 35.2 | 40.5 | 36.0 | 0.0 | 0.0 | 26.5 | 0.0 |
| $D_5$ (IC) | 5.0 | 5.0 | 5.0 | 0.0 | 5.0 | 5.0 | 0.0 |
| TD (h) (time delay) | | | | | | | |
| $TD_2$ | 0.33 | 0.32 | 0.14 | 0.044 | 0.36 | 0.075 | 0.025 |
| $TD_3$ | 1.8 | 1.2 | 0.44 | 0.0 | 0.0 | 0.1 | 0.0 |
| $TD_4$ | 3.66 | 2.44 | 0.80 | 0.0 | 0.0 | 0.425 | 0.0 |

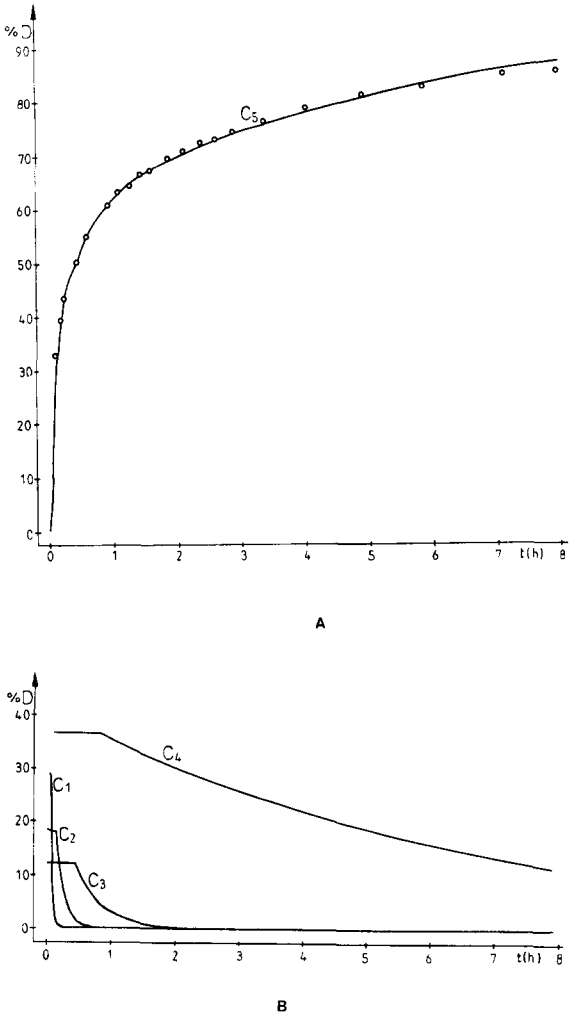


Fig. 4. Drug release profile for KG 100 chemiadsorbate (T = 37 ° C). A. Levels in sampling compartment; ○, experimental points, curve-model response. B. Simulated levels in carrier compartments.

strated. In Fig. 4A the experimental data points of the increasing drug concentration in the dissolution fluid are contrasted with the simulated release profile, based on the different processes ($C_1$–$C_4$), shown in Fig. 4B (in this figure the decreasing amount of drug in the single compartments versus time is given). In the temperature range under consideration (15–37 ° C) four different compartments C were identified, with an almost equal amount of the dose (quantity) of PHBAME. The time delays evaluated for the release from compartments $C_2$ to $C_4$ are possibly due to a change in the surface character of silica, in particular the wettability, as a consequence of the proceeding desorption process: surface-attached drug molecules may render the silica surface more or less hydrophobic. As a consequence the penetration of water into the pores may be delayed, until an initial cleavage of drug molecules changes the character of the surface again from hydrophobic to hydrophilic.

The desorption from the non-porous Aerosil 0 × 50 chemiadsorbate can be described by two releasing constants at 20 ° C. At 37 ° C, however, again four constants can be derived (Fig. 5, Table 2). This difference is still questionable and needs further research in the desorption process.

The difference of the chemiadsorbate release constants on porous and non-porous silica (Table 2) can be explained by the concept of surface fractals: the carrier with the larger fractal dimension $D$, KG 100 ($D$ = 2.56) may exhibit screening effects for water molecules, approaching the close vicinity of the surface-drug bond. This seems not to be the case on the 'flat' surface of Aerosil 0 × 50 with a fractal dimension $D$ of 2.00.

TABLE 3

*Summary of activation energies ($E_a$), activation entropies ($\Delta S^*$) and frequency factors ($A$) for drug release from chemiadsorbates with KG 100 and Aerosil 0 × 50 carriers*

| KG 100 PHBAME | | | | | Aerosil 0 × 50 | | |
|---|---|---|---|---|---|---|---|
| k (h) | $E_a$ (kJ/mol) | $r$ | ln $A$ ($10^{-3}$ $s^{-1}$) | $\Delta S^*$ (J/mol per K) | $E_a$ (kJ/mol) | ln $A$ ($10^{-3}$ $s^{-1}$) | $\Delta S^*$ (J/mol per k) |
| $k_1$ | 48.5 | 0.996 | 6.2 | −244.4 | 158.4 | 18.9 | −244.4 |
| $k_2$ | 78.4 | 0.971 | 9.1 | −244.7 | 269.0 | 30.5 | −244.3 |
| $k_3$ | 100.1 | 0.948 | 11.1 | −244.4 | | | |
| $k_4$ | 42.3 | 0.999 | 4.2 | −244.4 | | | |

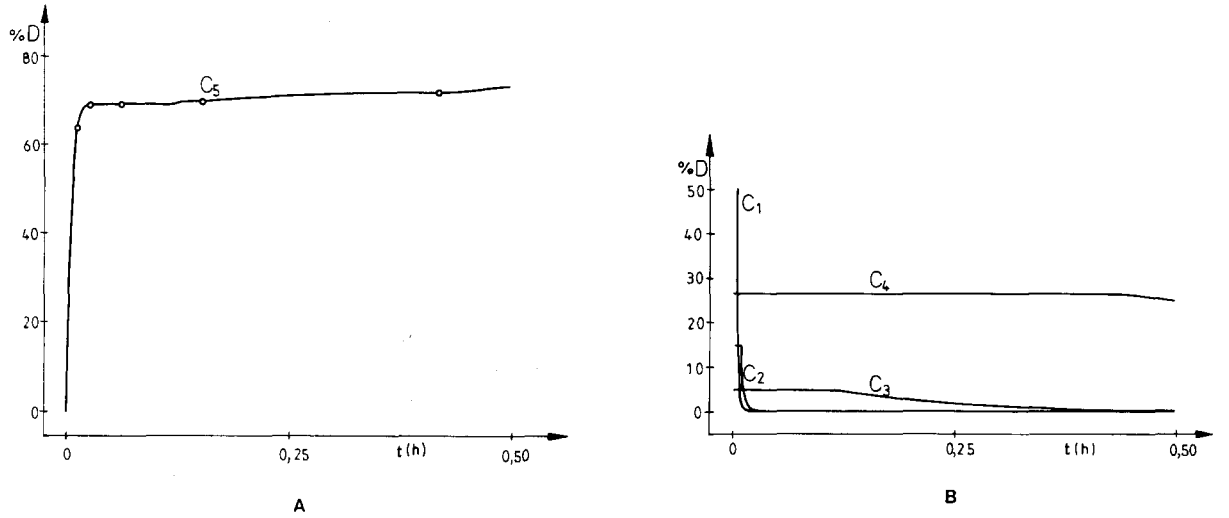


Fig. 5. Drug release profile for Aerosil 0 × 50 chemiadsorbate (T = 37 °C). A. Levels in sampling compartment; ○, experimental points, curve-model response. B. Concentration profiles in corresponding compartments.

The rate constants of release are increased on both the carriers by an increase of the temperature (Table 2). However, the large differences between corresponding k-values between the porous and the non-porous support still remain. Siegel and Langer (1986) introduced the mean first passage time (MFPT) to describe the random walk of drug molecules through porous frameworks (simulated by the Monte Carlo method). It is reasonable to assume that the real pore structure of KG 100 is very close to the random capillary model depicted in Fig. 6. With a rise in the desorption temperature the diffusion coefficient $D_{eff}$ is accordingly increased and as a consequence, the MFPT will increase.

The release constants at different temperatures were subjected to the Arrhenius plot exhibiting acceptable correlation coefficients (Table 3) in case of a porous carrier. With a non-porous carrier the parameters were calculated only with two temperatures.

A significant higher activation energy for the cleavage of the surface bond on the non-porous Aerosil 0 × 50 can be derived from this data. Again, this favors the view of the different fractal dimensions and their influence on the hydrolysis of the surface bonds, if the frequency factors $A$ are also introduced and taken into consideration. In contrast to the hydrolysis of the surface bonds on the non-porous support, exhibiting the usual energy barrier of the hydrolysis reaction, the cleavage in the porous support seems to be more influenced by the fractal nature of the pore walls. The transport of water molecules is obviously determined, hindered by caves, edges and holes in the size range of the chemiadsorbed molecules (Lill and Rupprecht, 1989). Finally, steric conditions in this local environment of the drug-silica bond may determine the probability of successful

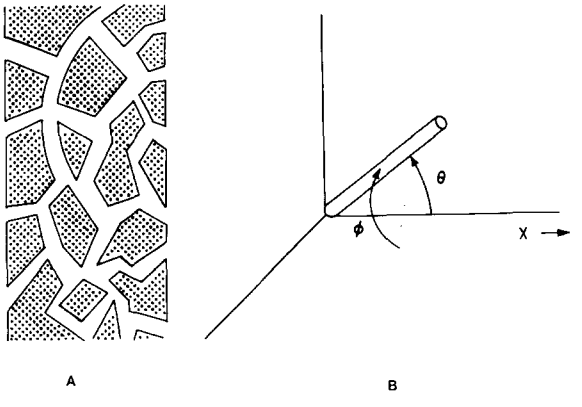


Fig. 6. Random capillary model (A), and parameters describing cylindrical pore orientation in the random capillary model (B) (from Siegel, 1988).

collisions with water molecules initiating hydrolysis.

The entropy of activation $\Delta S^*$ was calculated for 23 °C from the frequency factor ($A$) by means of Eqn 4 (Martin et al., 1983):

$$\Delta S^* = R \ln(\ln A - \ln kT/h) \quad (4)$$

where $k$ is Boltzmann's, and $h$ Planck's constant. No significant difference in the entropy of activation on both carrier materials was evaluated, supporting the view of a unique hydrolysis process of the surface bonds after collision with water molecules.

Summarizing, the drug release from chemiadsorbates on porous and non-porous silicas is determined by the cleavage of the silica-drug surface bond. A porous structure of the support seems to hamper the collision of water molecules with the surface bonds both by a restriction of the intimate 'reaction volume' and the proceeding transport processes. Further research is going on to verify this hypothesis.

## Acknowledgments

The authors wish to thank Degussa, Frankfurt (Germany) and E. Merck, Darmstadt (Germany) for their support to this research. Financial assistance from the Alexander von Humboldt Stiftung, Bonn and the 'Fond der Chemischen Industrie', Frankfurt is gratefully acknowledged.

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