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Chemisorbates of *p*-hydroxybenzoic acid methyl ester on silica as a new type of pro-drug IV. Drug release from chemisorbates dispersed in lipophilic vehicles

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Summary

The hydrolysis of the chemisorbate of *p*-hydroxybenzoic acid methyl ester (PHBAME) on porous silica (KG 100) incorporated in lipophilic vehicles such as liquid paraffin, synthetic oil Miglyol® 818 and white petrolatum was examined in dissolution media at pH 2 and 7.4, respectively. Chemisorbed PHBAME on KG 100 is released more rapidly in alkaline than in acidic dissolution fluids. Dispersions of the PHBAME-KG 100 chemisorbate in lipophilic vehicles modify the hydrolysis significantly. Drug release from chemisorbate dispersed in lipophilic vehicles may be controlled by the polarity of the vehicles. However, the viscosity of the vehicle, and not the polarity, exerts the strongest influence on the drug release.

Introduction

Among several approaches for improving the controlled release of drugs and drug targeting, the chemical linkage of active substances to organic polymer carriers has become an issue of increasing interest (Langer and Wise, 1984; Roche, 1987; Larsen et al., 1988; Mank et al., 1988; Larsen, 1989). However, inorganic carrier substances are only seldom used as carriers for chemically attached drugs (Rupprecht, 1983; Eckert-Lill, 1986; Eckert-Lill et al., 1987a,b).

The immobilized drug molecules on inorganic carriers are bound to the functional groups located on the outer (nonporous) or, in the case of porous carriers, the outer and inner surfaces of the particles. According to their promising physicochemical and physiological properties (Degussa, 1983), the most interesting inorganic carriers particles are silicas.

Chemisorbates on silica can be established by two types of surface linkages (Fig. 1): (i) drug or proper functional spacer molecules in between

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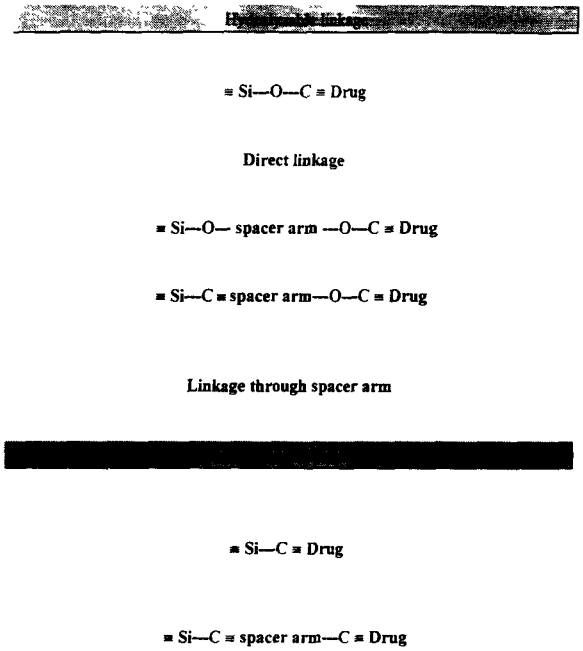

Fig. 1. Schematic representation of possible SiO_2 prodrug structure.

drug and silica are chemisorbed by nonhydrolyzable ≡Si–C≡ bonds by the reaction of organochloro or methoxysilane; (ii) the drug and/or proper spacer molecules are attached to the silica surface by the hydrolyzable ≡SiO–C≡ bonds, forming a surface ester of silicic acid (via the weak silanol groups).

The first type of linkage has successfully been applied in chromatography, catalysis, preconcentration of trace elements, ion exchange, biotechnology, and glass technology (Iler, 1979; Leyden and Collins, 1980; Airoldi and Concalves, 1987). Organo-modified silicas exibit interesting features for the stabilisation of pharmaceutical suspensions (Lee and Rupprecht, 1985). Silica particles are not absorbed through the intact stratum corneum (Rupprecht and Ferch, 1990). For this reason, they appear to be of great value as emulsion stabilizers (emulsifiers) (Sigg, 1991) and in particular in sunscreen preparations (Lill, 1985).

Drug molecules linked by surface ester functionalities can be cleaved in physiological fluids (gastrointestinal fluids) and can be used for both drug release modification and improvement of the dissolution of sparingly soluble drugs. This type of hydrolyzable chemisorbed drug also exhibits promising features for taste masking and chemical stabilisation of drugs.

The *p*-hydroxybenzoic acid methyl ester (PHBAME) linked by the phenolic hydroxy group to a porous silica carrier was used as a model of hydrolyzable chemisorbate. Preliminary experiments demonstrated that PHBAME is rapidly cleaved from the silica surfaces at pH values > 6. The rates of desorption (i.e., hydrolysis) of the surface ester bond and, consequently, the desorption of the cleaved molecules showed the same order of release as physiadsorbates of the drug on the same carriers (Eckert-Lill, 1986). In acidic solutions (pH < 3), however, drug cleavage is considerably retarded and prolonged (Eckert-Lill, 1986; Srcic and Rupprecht, 1991a).

During the adsorption and desorption experiments it is necessary to differentiate between the physically and chemically adsorbed state of PHBAME on silica. This is achieved by means of thermal analysis, DSC and TG (Srcic and Rupprecht, 1991a), and IR and UV spectroscopy (Lill and Rupprecht, 1989). NMR has also been employed to study chemisorbed molecules on silica (Slotfeldt-Ellingsen and Resing, 1980). The character of the silica sample surfaces was quantified by the fractal dimension, D, which exerts an important influence on the hydrolytic cleavage of chemisorbed species (Srcic et al., 1991).

To extend the hydrolysis process to acidic and especially to alkaline solutions, two strategies are considered (Fig. 2). First, the rate of drug desorption from physisorbates on silica can be reduced by the size of microporous silica and by hydrophobic coating of silica particles (Rupprecht et al., 1980). In this paper, the second strategy which features the incorporation of PHBAME-silica chemisorbates into oils and lipogels is described as an alternative to control drug release.

Materials and Methods

Materials

The following materials were obtained from the indicated sources and were used as received.

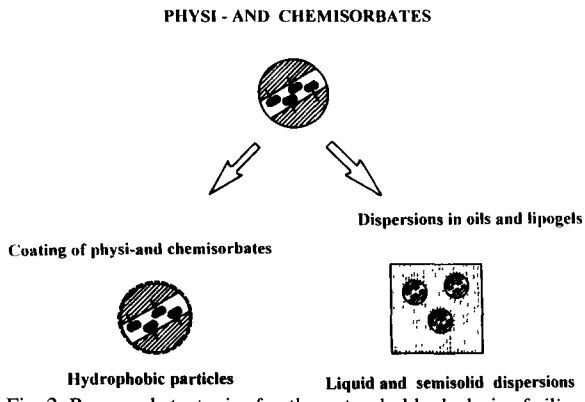

Fig. 2. Proposed strategies for the extended hydrolysis of silica chemisorbates.

Porous silica: silica gel KG 100 (E. Merck; mean pore diameter, 10 nm; specific surface area (BET, N_2), 300 m^2; particle size fraction, 200–500 μm; drug: *p*-hydroxybenzoic acid methyl ester, Nipagin M (corresponding to Pharm. Eur. II from Chemische Werke Hommel, Müllheim, Germany); lipophilic vehicles: liquid paraffin (corresponding to Ph. Jug. IV, available through Kemofarmacija, Ljubljana, Slovenia); synthetic oil: Miglyol® 818 (Hüls AG, Germany) and white petrolatum (corresponding to Ph. Jug. IV, available through Kemofarmacija, Ljubljana, Slovenia).

Methods

Preparation of chemisorbates

The preparation of PHBAME-KG 100 chemisorbates was carried out as described elsewhere (Eckert-Lill, 1986; Eckert-Lill et al., 1987a, 1988). The first important step of chemisorption is the activation of the silica surface by reaction with $SiOCl_2$. In this way highly reactive ≡Si–C≡ groups are formed on the surface. The second step was the addition of a cyclohexane solution of drug. After addition of catalytic amounts of pyridine and heating to 80°C, the surface links ≡Si–O–C≡ are formed by a nucleophilic S_{N2} substitution with the phenolic hydroxyl of the drug molecule. The solvent and the released HCl are removed by heating in vacuo (8 h, 100°C and about 8 mPa).

The chemisorbate contains 0.678 mmol PHBAME per g silica, corresponding to 2.5 mol drug per m^2. Considering the mean area occupied by one drug molecule (on a closely packed monolayer of flatly attached PHBAME molecules) of 60 $Å^2$, a surface density of 2.78 mol per g silica can be established. Consequently, the chemisorbate accounts for 90% of the maximum coverage.

Characterization of the chemisorbate

In addition to the methods mentioned above, the surface coverage was determined by elemental analysis and UV spectroscopy in the supernatant liquid after total hydrolysis of the chemisorbates in alkaline phosphate buffer solution (pH 7.4). Before use the chemisorbates were stored in a dry atmosphere (over silica gel).

Preparation of chemisorbate dispersions in oils

7% (white petrolatum) and 33% (liquid paraffin and Miglyol 818) dispersions of the chemisorbates in lipophilic vehicles were prepared manually by using a pestle and mortar. The dispersions were also stored in a dry atmosphere prior to the dissolution tests.

Determination of viscosity and water contact angles

The viscosity of lipophilic vehicles was determined on a rotational viscometer (RV 20, Haake Rotovisco, Germany) at 37°C, at a shear rate of 50 s^{-1}.

The contact angles between water and lipophilic vehicles were measured with a contact angle meter (Krüss, Germany) at room temperature. Contact angles of liquid paraffin and Miglyol 818 were evaluated from semisolids, formed after addition of gelling substance (10% of microcrystalline wax Esma M, W. Schluetter, Hamburg, Germany).

Drug release monitoring

A paddle apparatus (USP XXII) was used for following in vitro drug release. The dissolution fluids were 500 ml of 0.01 N HCl (pH 2) or 500 ml phosphate buffer (pH 7); stirring rate, 100 rpm; 37°C. Drug release was monitored in appropriate aliquots of the dissolution fluids in the UV range (255.5 nm) using a Perkin Elmer spectrophotometer (UV-Vis 554). Each aliquot was

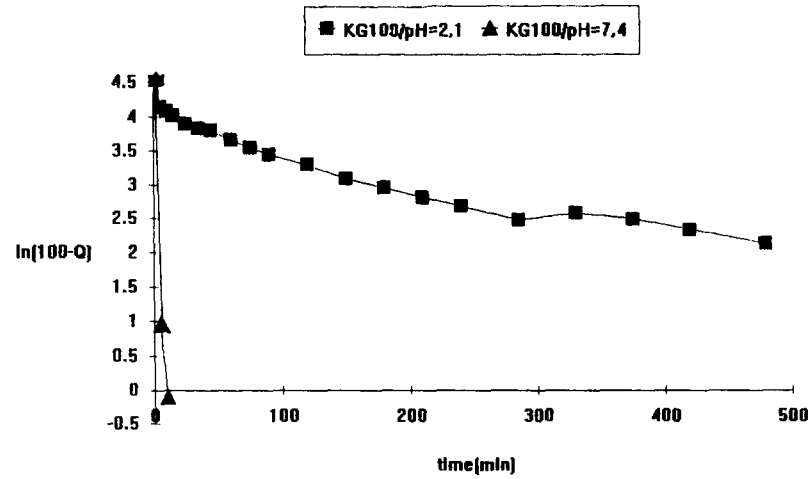

Fig. 3. Sigma-minus plot of hydrolysis of KG 100-PHBAME chemisorbate in acidic and alkaline dissolution fluids (pH 2.1 and 7.4, respectively).

substituted by an equal volume of fresh dissolution fluid.

Results and Discussion

The influence of pH on the rate of hydrolysis of PHBAME chemisorbates on silica in aqueous dissolution fluids is shown by sigma-minus plots in Fig. 3. In alkaline solution the chemisorbate is completly released within a few minutes. In acidic dissolution fluid, drug release is considerably slower and deviates from the linear behavior which would be observed in the case of a homogeneous pseudo-first order process.

This type of drug release observed can be explained by the fact that the ≡Si–O–C≡ surface bonds vary in stability. This is due to the fractal nature of the silica surfaces, offering a different local environment for the chemisorbed drug

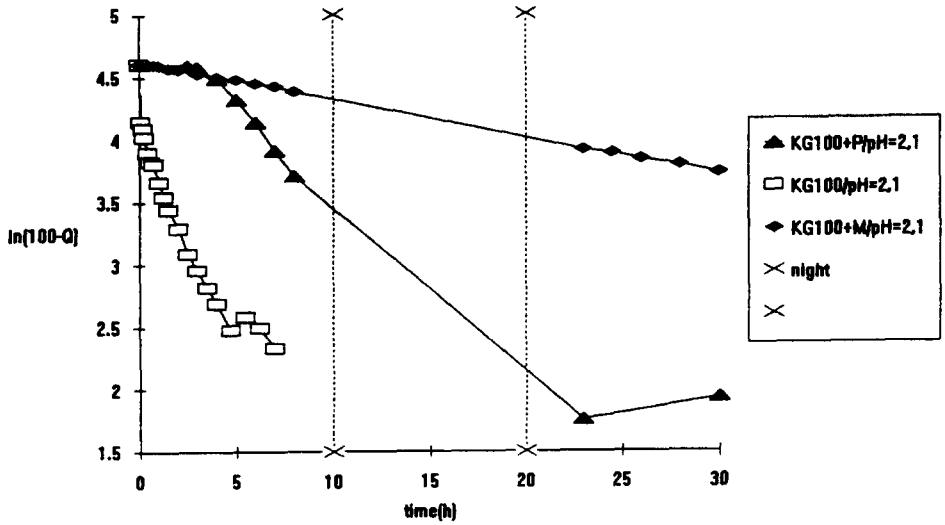

Fig. 4. Sigma-minus plot of hydrolysis of KG 100-PHBAME chemisorbate (KG 100) and its liquid paraffin (KG 100 + P) and Miglyol 818 (KG 100 + M) dispersions in acidic dissolution fluid.

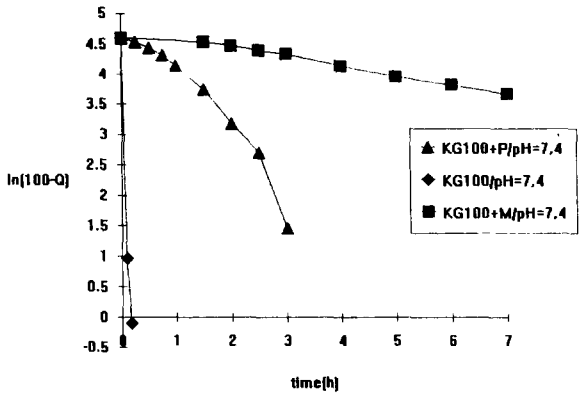

Fig. 5. Sigma-minus plot of hydrolysis of KG 100-PHBAME chemisorbate (KG 100) and its liquid paraffin (KG 100+P) and Miglyol 818 (KG 100+M) dispersions in alkaline dissolution fluid.

molecules. Modeling and simulation of the release process by an analog-hybrid computer confirms this view of PHBAME hydrolysis from silica chemisorbates.

In addition, at high surface coverage the rate of chemisorbate cleavage on silica is slower due to hydrophobic screening of the surface by the organic residues (Eckert-Lill, 1986; Eckert-Lill et al., 1987a). This effect may also contribute to the specific character of PHBAME release from the silica surfaces.

The contact angles of water on the lipohilic vehicles and their viscosities are listed in Table 1. Liquid paraffin and Miglyol 818 show the same viscosity but differ significantly in their contact angles with water. The lower contact angle of

TABLE 1

PHBAME released after 5 and 30 h of hydrolysis, contact angles with water and viscosity of lipophilic vehicles

Chemisorbate dispersed in	Hydrolysed after 5 h (%)		Hydrolysed after 30 h (%)		Θ (°C)	η (mPa s) ($50\ s^{-1}$)
	pH 2.0	pH 7.4	pH 2.0	pH 7.4		
Paraffinum liquidum	25.2	100	93.0	100.0	102.4 ± 5.4	26
White petrolatum	2.8	2.0	29.3	22.0	106.8 ± 2.9	976
Miglyol 818	12.3	47.4	58.7	100.0	79.5 ± 2.1	20

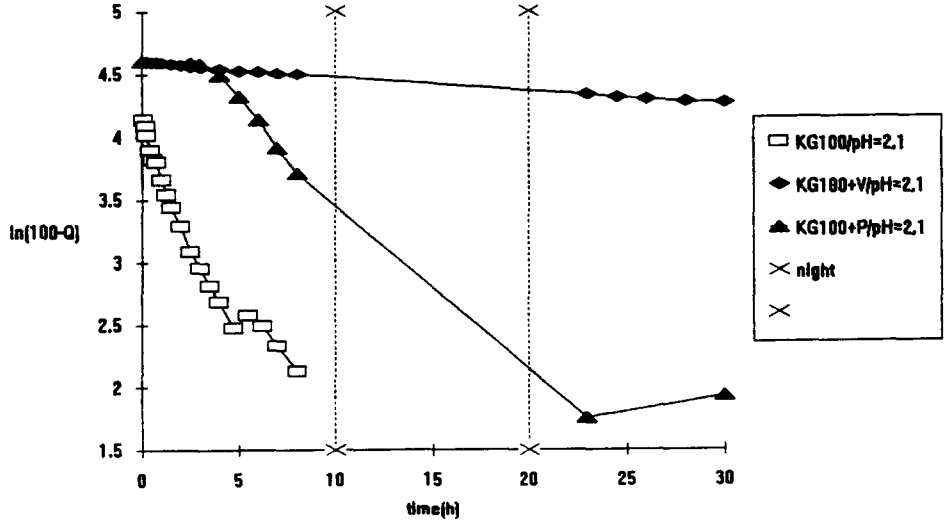

Fig. 6. Sigma-minus plot of hydrolysis of KG 100-PHBAME chemisorbate (KG 100) and its liquid paraffin (KG 100 + P) and white petrolatum (KG 100 + V) dispersions in acidic dissolution fluid.

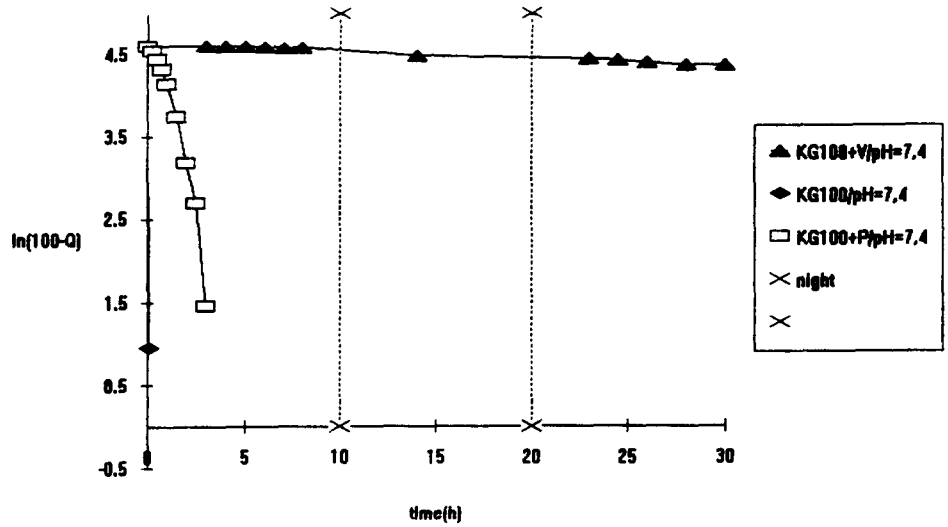

Fig. 7. Sigma-minus plot of hydrolysis of KG 100-PHBAME chemisorbate (KG 100) and its liquid paraffin (KG 100 + P) and white petrolatum (KG 100 + V) dispersions in alkaline dissolution fluid.

Miglyol 818 can be explained on the basis of the more polar nature of this fatty oil. However, Miglyol 818 retards drug release from the chemisorbate to a greater than liquid paraffin (Fig. 5). After 5 h, only 12% of the drug is released from Miglyol dispersion while 25% is released from the paraffin dispersion during the same time (Table 1). The dissolution rates in alkaline fluid are up to 4-fold faster than in the acidic fluid (Fig. 5 and Table 1). However, for Miglyol and liquid paraffin dispersions the ratio of hydrolysis is the same as in the acidic dissolution fluid.

Due to their chemical nature, the contact angles of white petrolatum and liquid paraffin with water are nearly identical. In contrast, the hydrolysis patterns of PHBAME release from the chemisorbate dispersions show a considerable difference (Figs 6 and 7). Obviously, the viscosity of the dispersion media determines the kinetics of drug release. The considerably greater viscosity of white petrolatum may influence different pro-

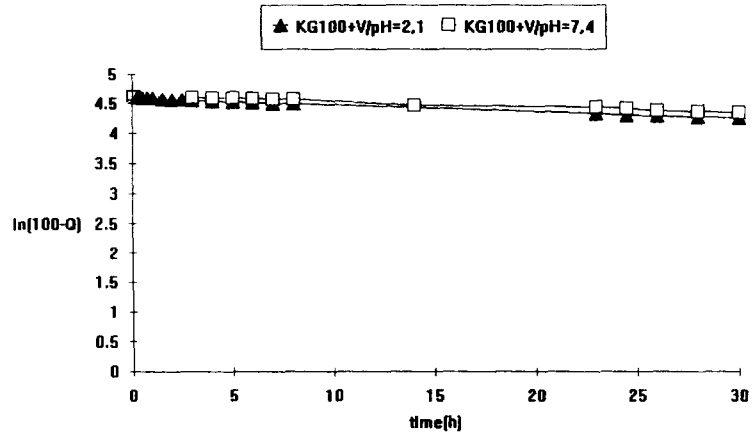

Fig. 8. Sigma-minus plot of hydrolysis of KG 100-PHBAME chemisorbate dispersios in white petrolatum in acidic and alkaline dissolution fluid.

cesses such as the penetration of water molecules to the carrier surface with the chemisorbed drug molecules and the diffusion of the released drug from the carrier into the dissolution fluid. Consequently, the different rates of hydrolysis in acidic and alkaline dissolution fluids no longer have any significant influence on the release from the white petrolatum dispersion (Fig. 8).

Conclusions

(i) Chemisorbed PHBAME on silica (KG 100) is released more rapidly in alkaline than in acidic dissolution fluids; (ii) dispersions of PHBAME-silica chemisorbates in lipophilic vehicles such as liquid paraffin, Miglyol 818 and white petrolatum modify drug release significantly; (iii) drug release from chemisorbate dispersions in lipophilic vehicles can be controlled by the polarity of the vehicles; and (iv) the viscosity of the lipophilic vehicles influences drug release more than the polarity, as determined from the measurements of the contact angle with water.

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