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DRUG RELEASE FROM COADSORBATES OF NONIONIC SURFACTANTS WITH PARABENES ON POROUS SILICA SUPPORTS

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ABSTRACT

Parabenes are coadsorbed from aqueous solutions with nonionic surfactants (polyoxyethylene-nonylphenols) on silica surfaces. Rate and extend of parabene desorption from corresponding coadsorbates on porous silica were shown to be dependent on the influence of structure and pore size (in the mesopore range 2 - 10 nm) of the silica supports, the alkyl chain length of the parabenes, the structure of the

POE-surfactant, and the adsorption equilibria established during the drug loading of the supports. The consequences of coadsorption on drug release modification are discussed.

INTRODUCTION

Silicas are recommended as drug supports in pharmaceutical preparations due to their excellent physiological and physico-chemical properties [1]. Porous silicas effectively modify the release of incorporated or adsorbed drugs. Active substances (i.e. griseofulvin) which adsorb onto silica surfaces negligibly from aqueous solutions have enhanced dissolution rates from silica adsorbates, containing pores > 10 nm [2]. Cationic and aggregating substances which are strongly bond to the silica surfaces from aqueous solutions show a prolonged release from their adsorbates on porous silica with pores smaller than 8 nm. They exhibit interesting features for drug release modification [3].

Recently it was observed that nonionic surfactants attract small drug molecules (i.e. para-hydroxybenzoic

acid alkylesters = parabenes) to their adsorption layers on silica from aqueous solution. This is even the case when these drugs are not adsorbed on silica from their pure solutions [4]. This coadsorption phenomenon has been compared with the solubilization of such drugs into surfactant micelles in the liquid phase [5]. The structure of the corresponding coadsorbates was discussed in view of the hemi-micelle concept, presented by Fuerstenau [6]. The drug molecules are supposed to be attached parallel with their ring system and their alkyl chains to the hydrophobic moieties of the surfactant molecules which are adsorbed via their POE chains to the carrier surface.

In this paper in-vitro studies on the desorption (dissolution) of a series of parabene nonionic surfactant coadsorbates are presented so as to evaluate their possible use in drug release modification. They are coadsorbed to silicas with different pore sizes and structures by polyoxyethylene-nonylphenols and polidocanol.

EXPERIMENTAL

A) MATERIAL

a) Supports:

silicas precipitated; pore diameter(d_{pore}) 2 nm

(KG 20), 4 nm (KG 40), 6 nm (KG 60), 10 nm (KG 100) [E.Merck, Darmstadt, Germany]

silica Kr 36: obtained by hydrolytic polycondensation of polyethoxysiloxane; d_{pore} 14 nm [7].

b) Surfactants:

polyoxyethylene-nonylphenols: POE chain length (average): 9.4 ; 12.7; 21.2 ; 50 [Marl, Hüls, Germany]; Polidocanol (polyoxyethylene-9-dodecanol) [Desitin Werk, Hamburg]

c) Drugs:

p-hydroxybenzoic acid-ester: methyl-, ethyl-, propyl- [Nipa-Laboratories, Hamburg, Germany]

B) PREPARATION OF COADSORBATES:

Suspensions of silica (4 g in 100 ml liquid phase) in surfactant-parabene solutions (concentrations adjusted according to adsorption isotherms, as previously reported [4] were shaken at 20° C for 16 h to maintain well defined adsorption equilibria. After separation from the liquid phase by filtration the silica coadsorbates were dried over P_2O_5 (50° C, 48 h). The drug and surfactant contents of the coadsorbates was determined from:

a) the equilibrium concentrations in the supernatant of the suspensions described above and,

b) the total desorption of the adsorbates with ethanol.

Simultaneous determination of drug and surfactant by HPLC:

liquid phase: methanol/H_2O 85:15;

column : RP 18 silica;

detection : UV absorption at 277 nm;

equipment : Perkin Elmer HPLC Series 2 + Uvicon LCD 725, LKB)

C) DESORPTION EXPERIMENTS:

Dissolution test (apparat. II, USP XXII suppl. 3): 500 ml H_2O; 37 ± 0.2°C; 50 rpm, adsorbate 500 mg. Monitoring of concentration: HPLC-analysis of samples (0.5 ml) over 6 h.

RESULTS AND DISCUSSION

The in-vitro drug release was studied on coadsorbates of parabenes with poloxyethylene surfactants

following the results of preliminary adsorption experiments [4]. The coadsorbates were obtained by establishing adsorption equilibria from solution in such a way that a sufficient amount of drug was adsorbed onto the silica supports while the corresponding equilibrium concentration of the drug in the supernatand was very low. As a consequence coadsorbates could be obtained where the drug content originated almost quantitatively (> 95%) from adsorption equilibria. Any artefacts due to deposited drug after drying of the adsorbates from adhering drug solution after the separation step could be avoided (TAB. 1+2). Rate and extent (pharmaceutical availability) of drug liberation were recorded, varying important parameters of the supports, the coadsorbing surfactants and the drug models.

1) Influence of the silica structure on drug release

From the coadsorbates with POE-9.4-nonylphenol (TAB. 1) it can be seen that ethylparabene desorbs with different release patterns, depending on the pore structure and size of the silica supports (FIG. 1).

A sudden release of the active component is shown by the wide-pore silicas KR 36 ($d_{pore} \approx 15$ nm, spherical

TABLE 1

Ethylparaben-POE-(9.4)-Nonylphenol Coadsorbates on Porous Silicas

Silica	Coadsorbate composition					
	ethylparabene			POE-(9.4)-nonylphenol		
	$\mu mol \cdot g^{-1}$	$\mu mol \cdot m^{-2}$	$mg \cdot g^{-1}$	$\mu mol \cdot g^{-1}$	$\mu mol \cdot m^{-2}$	$mg \cdot g^{-1}$
Kr 36	29.5	0.0578	4.90	409.9	0.794	255.1
KG 100	36.9	0.123	6.13	496.8	1.350	313.0
KG 60	37.0	0.074	6.15	497.5	0.997	313.4
KG 40	36.65	0.056	6.09	497.1	0.765	313.2
KG 20	7.98	0.010	1.33	145.3	0.193	91.5
KG 40	43.1	0.066	7.15	adsorption from 1.2-dichloroethane		

TABLE 2

Composition of Coadsorbates of POE-nonylphenols with Parabens on Porous Silica KG 40

A) Coadsorbates of ethyl-parabene with POE-(x)-nonyl-phenols				
Adsorbed amount of	x=9.4	x=12.7	x=21.2	x=50
ethylparabene µmol/g	36.65	30.17	28.0	13.3
mg/g	6.09	5.01	4.65	2.17
POE(x)nonylphenol µmol/g	497.1	326.0	236.2	99.8
mg/g	313.2	254.3	274.0	246.5

B) Coadsorbates of POE-(9.4)-nonylphenol with alkyl-parabenes			
Adsorbed amount of	methyl-	ethyl-	propyl-
POE (9.4) nonylphenol µmol/g	477.7	497.1	489.1
mg/g	300.9	313.2	308.1
paraben µmol/g	32.25	36.65	40.63
mg/g	4.92	6.09	7.32

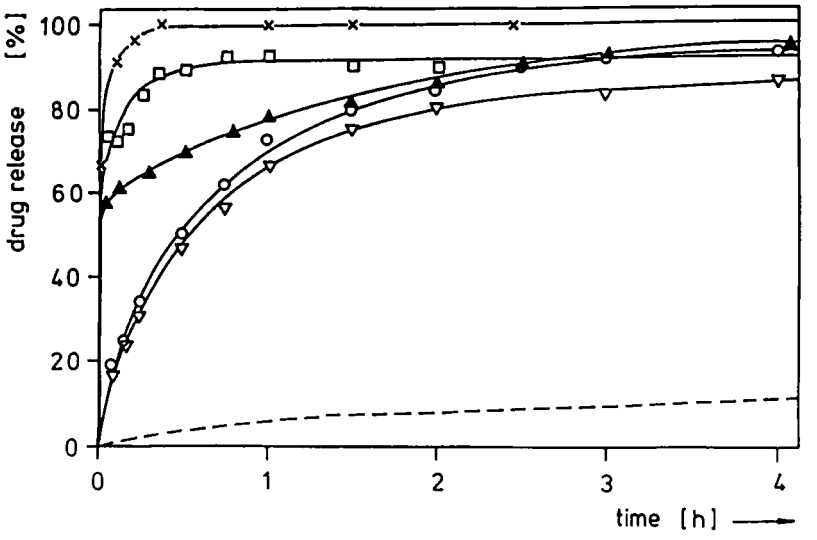

FIGURE 1

Release of Ethylparabene from Coadsorbates with POE-(9.4)-nonylphenol on Porous Silicas with Different Pore Structure

X———X KR 36 and physiadsorbate of ethylparabene on KG 40
□———□ KG 100
▲———▲ KG 60
▽———▽ KG 40
O———O KG 20
- - - - - - desorption of POE-(9.4)-nonylphenol from KG 60

particles with an inhomogenous pore size distribution) and KG 100 and KG 60 ($d_{pore} \approx$ 10 nm and 6 nm, respectively; both containing of particles with a homogenous pore size distribution). Within 3 min. 60 - 80% of the coadsorbed ethylparabene is released in water.

Drug release from coadsorbates on KG 40 ($d_{pore} \approx 4$ nm) and KG 20 ($d_{pore} \approx 2$ nm) appears to be obviously controlled by matrix diffusion with practically the same half-life (30 min.) and only small differences in availability.

For comparison the simultaneous desorption of the surfactant is a long term process, with only 10% of the adsorbed amount being released within 4 hours. This is a consequence of the strong adsorption of the surfactants to the silica surface, leaving only very small concentrations of free surfactant in the equilibrium. A physiadsorbate of ethylparabene without surfactant on porous silica (KG 40), prepared by the solvent deposition technique from nonpolar 1,2-dichloroethane, releases the drug completely within 15 min.

As a result, KG 40 was selected as the most promising support to optimize drug release and to study the influence of surfactant and drug structure. (On KG 20 pore exclusion by narrow pores is a limiting factor of coadsorption.)

2) Alkyl chain length of parabenes

The influence of drug molecule properties on the desorption from coadsorbates on silica was studied by

comparing the corresponding dissolution pattern of parabenes with different alkyl chain length in the ester group. The in-vitro release of the parabene-POE-(9.4)-nonylphenol coadsorbates on KG 40 is contrasted in FIG. 2 : Increase in the hydrophobic moiety of the drug molecule decreases the rate of release. The half life of desorption changes from 22 min. for the methyl- to 35 min. for the ethyl- and, finally, to 85 min. for the propylparabene. The extensions of the alkyl chain also reduce the available amount of drug after 4 hours with 95% for methyl- to 84% for ethyl- and 72% for propylparabene.

From the beginning, the drug desorption from coadsorbates on silica follows a linear relationship between drug release and the square root of time. After 65-70 % release of the coadsorbed drug the desorption process is increasingly delayed. The linear part of the desorption curves can be interpreted in analogy to the matrix liberation concept presented by Higuchi [8], where the desorbed amount, M, is given by:

$$M = \left(\frac{\varepsilon}{\tau} D\ C_s(2A-C_s)\ t\right)^{1/2}$$

with ε the porosity of the matrix, τ the tortuositiy

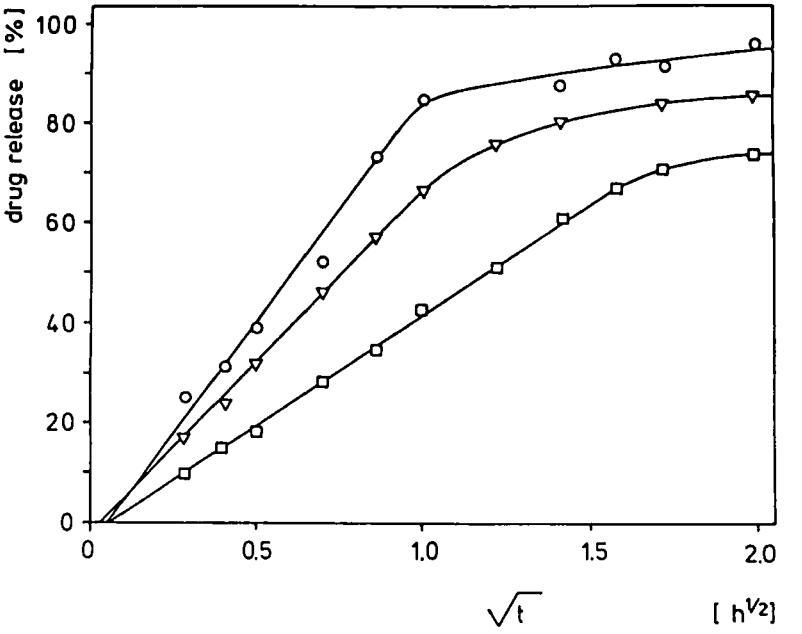

FIGURE 2

Release of Alkyl Parabenes from Coadsorbates with POE-(9.4)-nonylphenol on KG 40

	Drug content [mg·g^{-1} SiO_2]
O——O methylparabene	4.92
▽——▽ ethylparabene	6.90
□——□ propylparabene	7.32

factor of the pores, D the diffusion coefficient, A the adsorbed amount of drug and C_s the concentration of the parabene in the adsorption equilibrium of the coadsorbate inside the matrix.

Assuming a reversible ad- and desorption of the parabenes in the systems considered here, it is evident

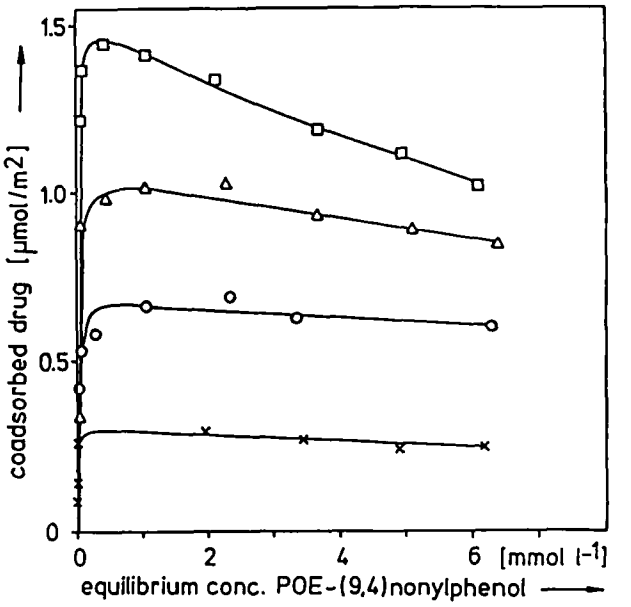

FIGURE 3

Coadsorption of p-Hydroxybenzoic Acid and Alkyl-Parabenes with POE-9.4-nonylphenol on KR 36. Total Concentration of Drug 1 mmol l^{-1}.

X——X p-hydroxybenzoic O——O methylparabene
Δ——Δ ethylparabene □——□ propylparabene

from the adsorption isotherms (FIG. 3) that the equilibrium concentration of the surfactant is very low and almost constant. The corresponding concentration of drug in the supernatant is also very low and decreases linearly during the desorption process [4]. For the first 30% of adsorbed drug the "high affinity isotherm conditions" are fulfilled. The additional retarding

effect at the end of the desorption process is probably due to a rapid fall of the equilibrium concentration of the adsorbed drug inside the porous matrix.

3) Ethylparabene release from coadsorbates with different POE-surfactants

In FIG. 4 the release of ethylparabene from coadsorbates with POE-nonylphenols of different POE chain length and with polidocanol, (POE-9-dodecanol) on silica KG 40 are contrasted:
In the series of the POE-nonylphenol surfactants the half life of desorption decreases with increasing chain length of the POE surfactant entity from 35 min. for the 9.4- to 10 min. for the 50-homologue.

Higher rates of drug desorption from coadsorbates with surfactants exhibiting larger hydrophilic POE moieties correlate with the tendency of the surfactants to attract the drug into the coadsorbates [4]. This is expressed quantitatively by the adsorption equilibria, which, as discussed above, determine the rate of desorption following the matrix release concept.

Only a minor influence is observed for different structures of the hydrophobic surfactant moiety. Coad-

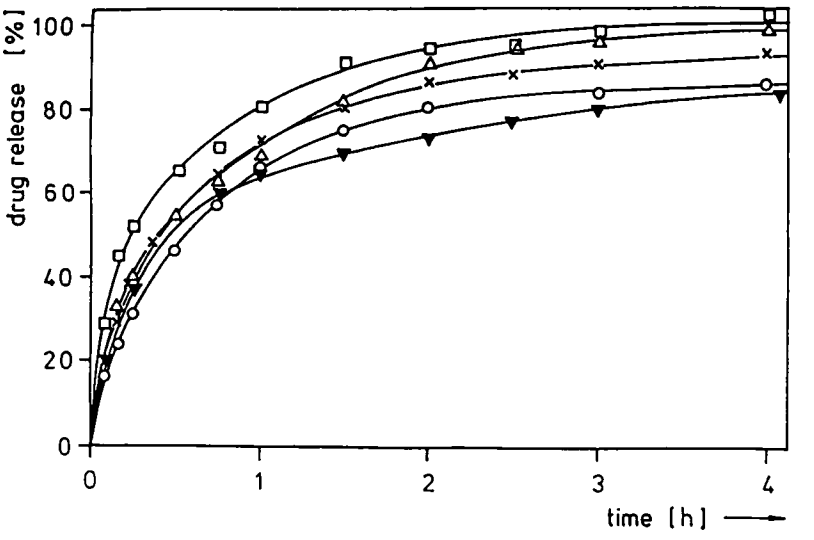

FIGURE 4

Release of Ethylparabene from Coadsorbates with POE-Surfactants on KG 40;

Coadsorbing surfactant:

		Drug content [mg·g^{-1} SiO_2]
O——O	PEO-9.4-nonylphenol	6.90
X——X	PEO-12.7-nonylphenol	5.01
Δ——Δ	PEO-21.2-nonylphenol	4.65
□——□	PEO-50-nonylphenol	2.17
▼——▼	polidocanol	6.20

sorbates of ethylparabene with polidocanol, a POE-9-dodecanolether, show almost the same release pattern as the corresponding POE-9-nonylphenol coadsorbate (FIG. 4).

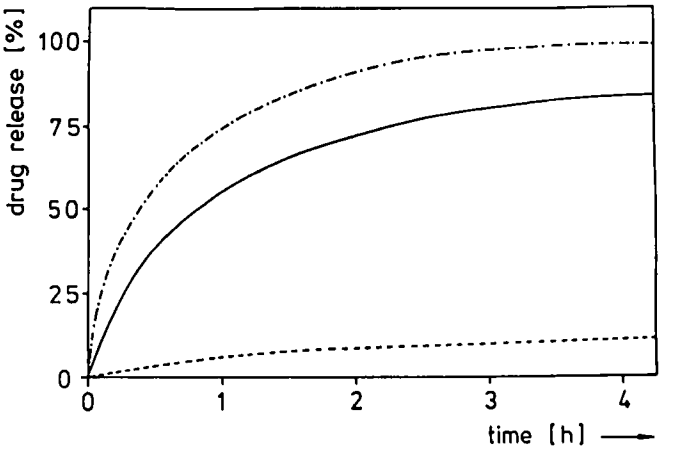

FIGURE 5

Release of Ethylparabene from Coadsorbates with POE-9.4-Nonylphenol on KG 40, depending on the Surfactant Concentration during the Preparation of the Adsorbates

—·—·—·— equilibrium concentration surfactant < CMC; drug content 4.8 $mg \cdot g^{-1}$ SiO_2
——— equilibrium concentration of surfactant > CMC; drug content 5.8 $mg \cdot g^{-1}$ SiO_2
– – – – – POE-9.4-nonylphenol

4) Adsorption equilibria during loading of the adsorbates

Rate and extend of ethylparabene desorption from POE-surfactant coadsorbates on silica can be adjusted by the surfactant concentration during the adsorption step. Coadsorbates obtained from surfactant concentrations below the CMC, release the drug faster than those obtained above the CMC (FIG. 5). The half life of

desorption increases from 10 min. to 50 min., and the availability after 4 hours decreases from 96% to 81%.

These differences are due to the higher amount of adsorbed surfactant in the coadsorbates which are present, if the CMC is exceeded during the adsorption step. After immersing the coadsorbates into the dissolution fluid, water penetrates into the pores of the support and a desorption equilibrium is established. Adsorption above the CMC must consequently lead to a higher surfactant concentration inside the pores during the desorption process, where the adsorbed surfactant and, probably, surfactant aggregates in the liquid phase hinder the desorption of the drug by binding.

CONCLUSIONS

Parabenes which are coadsorbed by nonionic surfactants onto porous silicas show a delayed desorption in aqueous solution. The rate of desorption is influenced by:

a) the pore structure of the support, with an effective retardation exhibited by silicas with pores ≤4 nm.

b) the surfactant and the drug structure: an increase in lipophilic properties - decrease of POE chain length of the surfactant or increase of alkyl-entities of the drug molecules - decreases the rate of desorption. The amount of desorbed surfactant remains very low during the desorption experiments (< 3% within 5 h).

The described coadsorption systems - porous silica, nonionic surfactant, parabenes - show some features of common interest:

a) The release rate of drugs can be modified (reduced) by combination of porous matrix supports with surfactants, if coadsorption of the drug is observed.

b) The described coadsorbates can be easily prepared and are stable on storage.

c) The effects described above should also be considered if the drug release from porous dosage forms (pellets, tablets,..) with incorporated wetting agents (surfactants) is discussed.

d) The absolut amounts of coadsorbed drug are in the range of 1-40 $mg \cdot g^{-1}$ carrier. These amounts are small and not interesting for a great number of active substances, used in oral dosage froms with prolonged action. However, this principle may be of some interest for high efficient, very low dosed drugs in solid dosage forms. Apart from the problem of the modified release the uniform distribution of active substances in single dose units can be elegantly achieved by the coadsorption method: The drug is distributed in the adsorbates on a molecular level, and, consequently an optimum of equal dosage is guaranteed. In contast to the usual method of solvent deposition organic solvents are not necessary and drug release can be better adjusted.

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