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The use of porous and surface modified silicas as drug delivery and stabilizing agents

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I. Introduction

Amorphous colloidal and porous silicas are widely used as adjuvants in drug preparation and pharmaceutical analysis (1,2,3). Among the broad scale of applications, their stabilizing and drug-release qualities (4,5) have been the source of further investigation in this field including the introduction of new starting materials and production techniques as well as organo-modified silicas. Consequently drug retardation on the basis of silica-embeddings and high efficient gelling silicas have been developed.

II. Results and discussion

1. Development of SiO_2 embeddings for controlled drug release

Inspired by a technique for the production of coated glass beads, used in chromatography (3), we developed a variety of methods to incorporate drugs directly into porous silica envelopes with controlled pore structure. In this way a better control of drug release is achieved than is shown by drug adsorbates on commercially available porous silicas (6) or similar types of nonsoluble, hydrophilic and porous matrices (7).

1.1. Chemical principles of embedding or coating

The coating or embedding of drugs with porous silica is based on a two step process of hydrolytic polycondensation of tetraethosysiloxane (8) as the starting material (fig.1):

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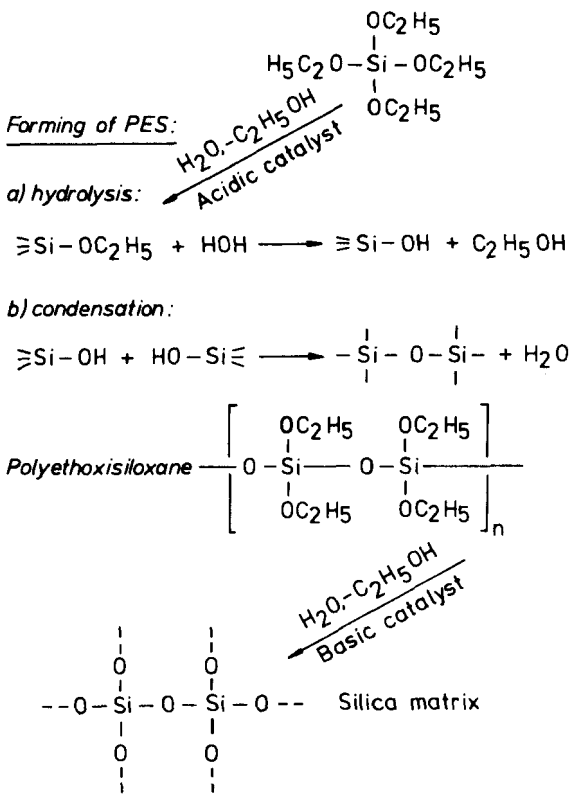


Figure 1

Firstly tetraethoxysiloxane is partially hydrolyzed and then partially condensed in the presence of acidic catalysts such as hydrochloric acid, forming a viscous liquid, polyethoxysiloxane (PES). The viscosity of PES increases exponentially with the mean molecular weight of the polymer (10 mPa·s - 20 000 mPa·s over the range of 750 - 2800). The viscosity is thus a sensitive parameter for the characterisation of the degree of polymerisation, which depends on the amount of water and catalyst added to the reaction mixture.

Secondly, the drug is incorporated into the viscous PES as crystal particles, as droplets or as solution and, after homogenization of the dispersions, the polycondensation proceeds by addition of basic catalysts and water. After completion of the hydrolytic polycondensation of the polymer the solid, porous silica envelope or matrix is obtained, whereby ethanol is set free. The pore structure of this silica material is determined by the

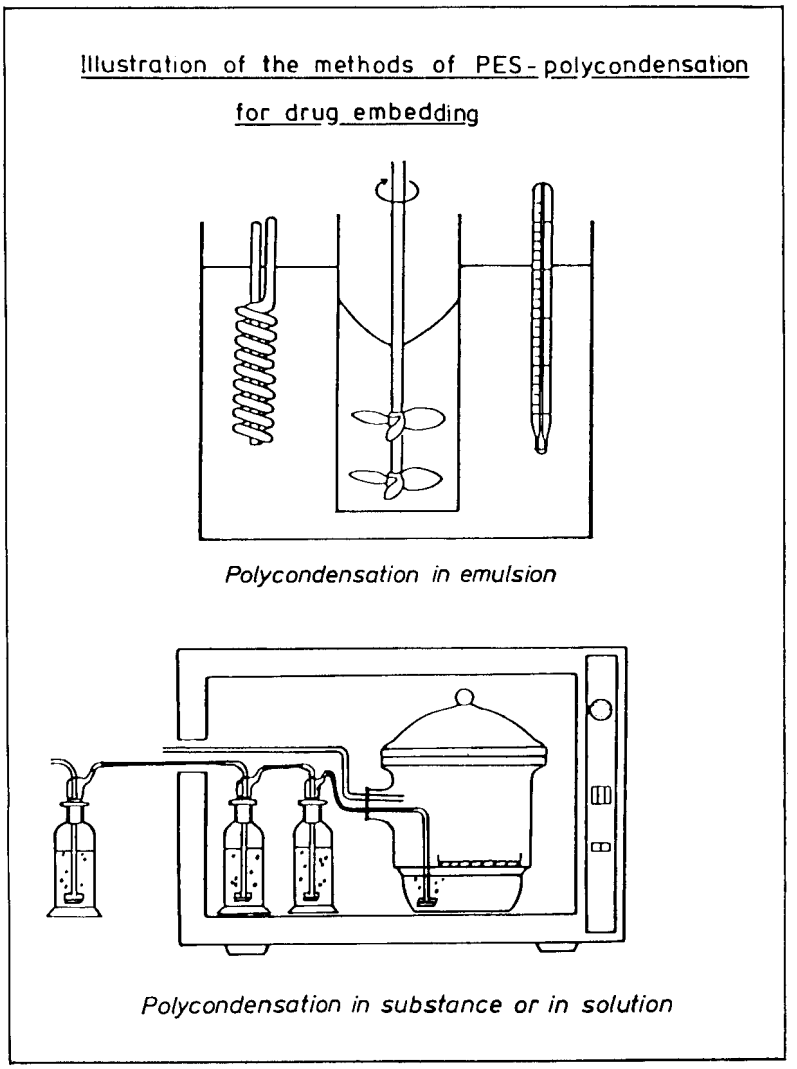


Figure 2

following parameters: The type and concentration of the catalyst, the degree of polymerization of the PES, the water available and the reaction temperature. In this way, the mean pore diameter can be reproducibly controlled in the range from micro- to macropores (i.e. 1-1000 nm) (8).

1.2. Production techniques

For the preparation on the level of laboratory products different methods were developed for drug-silica embedding, as given schematically in fig. 2 :

Polycondensation in emulsion
Polycondensation in substance
Polycondensation in solution

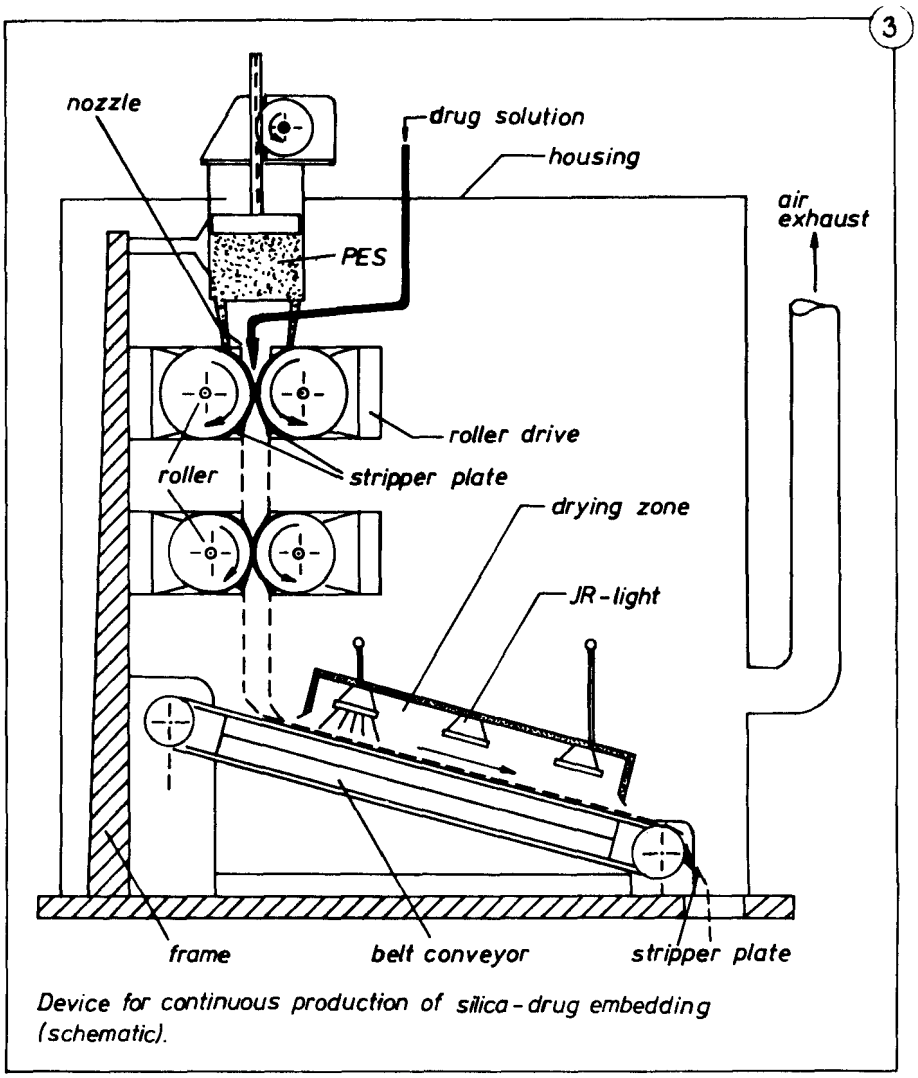
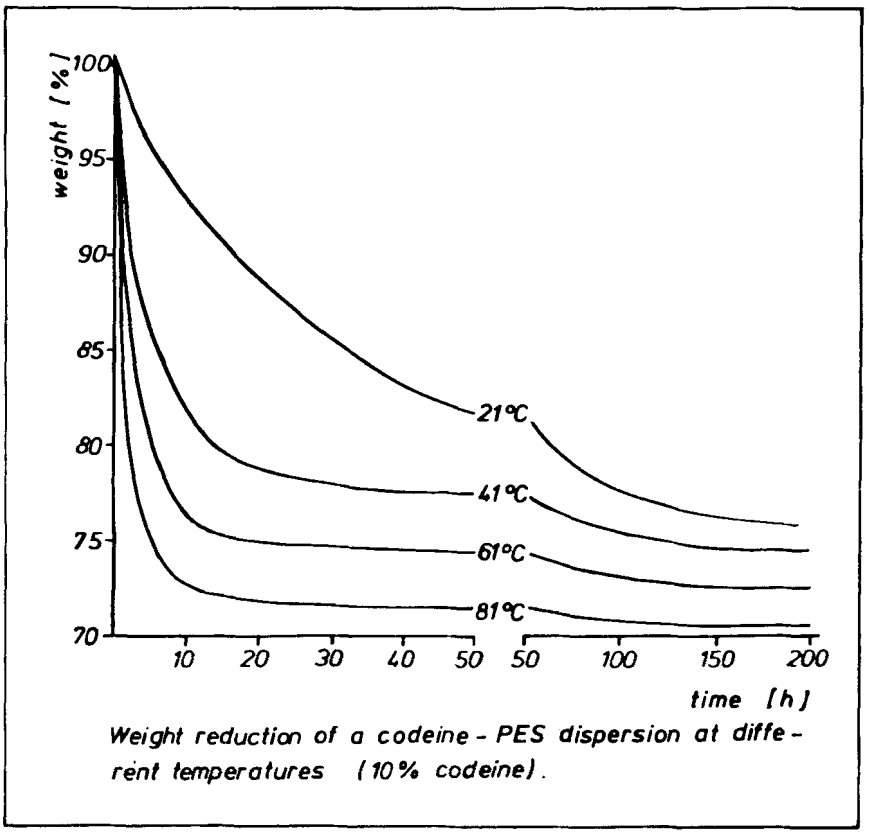


Figure 3

1.2.1. Polycondensation in emulsion

The technique of polycondensation in emulsion starts with a dispersion of a mixture of the drug (particles or liquid) and PES in an aqueous medium (or some other appropriate liquid, in which the drug should be insoluble). On stirring of the dispersion, the drug-PES mixture forms spheres, whose mean particle size depends on the stirring rate and the dimensions of the reaction vessel. After addition of an (external) catalyst such as ammonia the droplets are solidified by the hydrolytic polycondensation, leaving the porous silica envelopes. Finally the spheres are separated from the dispersion liquid by sieving, rinsed with water and then dried.



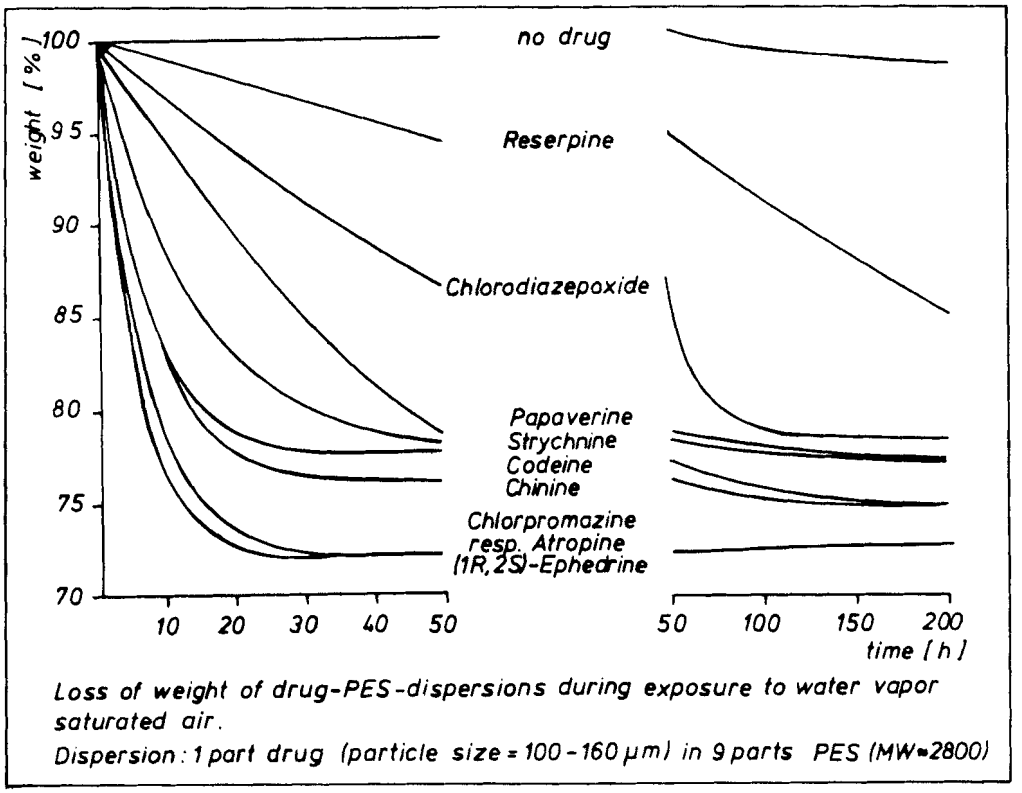
Weight reduction of a codeine - PES dispersion at different temperatures (10% codeine).

Figure 4

1.2.2. Polycondensation in substance

Polycondensation in substance is easier to perform with small batches. Again the drug is carefully dispersed in PES of sufficient viscosity to obtain stable and homogenous suspensions or emulsions of the drug in PES. These dispersions are exposed in thin layers (maximum 5 mm) to an atmosphere with a defined content of water vapour and, if necessary, a volatile catalyst (ammonia), under controlled temperature.

During polycondensation, a precise control of the temperature is not possible with voluminous batches, since the heat generated by the polycondensation reaction is accumulated in the material, mainly due to a decreasing thermal conductivity of the solidified, porous material. At higher condensation temperatures the polycondensation is enhanced, forming larger pores so that the release rate of the incorporated drug proves to be non-uniform in such batches.

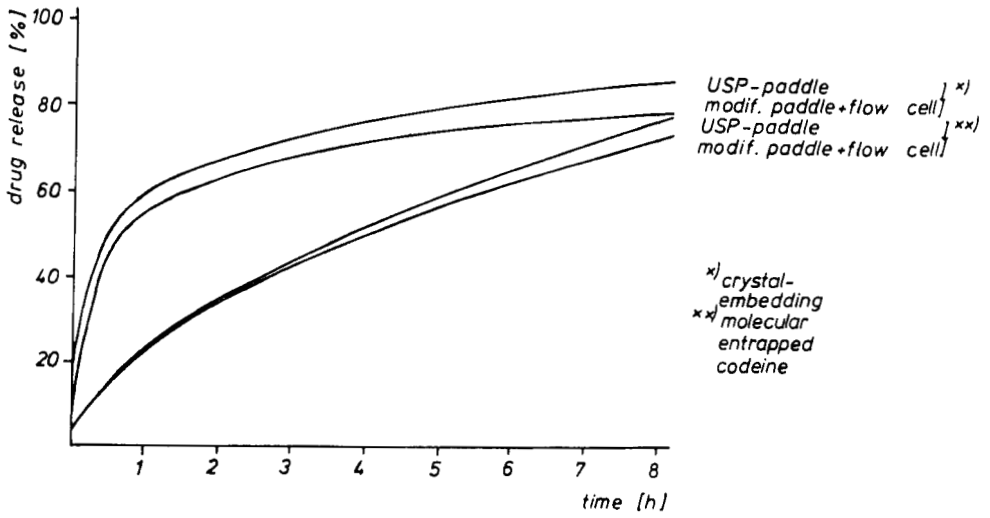


Loss of weight of drug-PES-dispersions during exposure to water vapor saturated air.
Dispersion: 1 part drug (particle size = 100-160 µm) in 9 parts PES (MW≈2800)

Figure 5

Drugs (bases)	pK_B		Solubility (T= 21°C) in PES ($c_{30\,min}$)	Time for attaing 50 Pas in PES-drug dispersions
	pK_{B1}	pK_{B2}	MG subst. in 1 ml	min
1 (1R,2S)-ephedrine	4,6	–	76,6	0,3
2 chlorpromazine	4,7	–	62,2	1,6
3 atropine	4,3	–	24,8	2,0
4 codeine	6,1	–	15,8	9,5
5 quinine	6,0	9,9	11,6	11,9
6 eserine	6,1	12,2	10,4	18,9
7 strychnine	6,0	11,7	1,37	34,5
8 papaverine	8,1	–	1,86	–
9 R-adrenaline	2,0	3,8	0,004	–
10 chlordiazepoxide	9,2	–	0,93	–
11 reserpine	7,4	–	0,036	–

Figure 6



Codeine-release from silica embeddings. Comparsion of "in-vitro"-methods.

Particle size of embedding: 500-800 µm

Dissolution fluid: HCl/KCl-buffer pH 2, ion strength 0,1, T=37 °C

Figure 7

1.2.3. Polycondensation in solution

Polycondensation in solution is achieved under the same conditions as polycondensation in substance, but it starts with a mixing of PES with a solution of the drug in an appropriate solvent, giving a molecular scale entrapment of the drug in the polymer. Again the size of a batch is limited by heat conductance problems. The hard and brittle material obtained by polycondensation in substance and in solution can easily be crushed to the desired particle size and then sorted by sieving.

1.2.4. Continous production

To overcome the problem of inhomogenously condensed material a continous production of PES drug dispersions and subsequent polycondensation can be used, as given schematically in fig. 3. Drug (solution) and PES are simultanously run through roller pairs with different rotational speeds (similar to ointment mills) to obtain a sufficient mixing of the components. Then the material is brought onto a conveyor belt, where the polycondensation is carried on under a stream of water vapor and, if necessary, ammonia. IR-sources over the conveyor belt heat and then dry the material. The conveyor speed is adjusted in such a way, that the PES-drug dispersion leaves the belt as plastic sheets. These can be

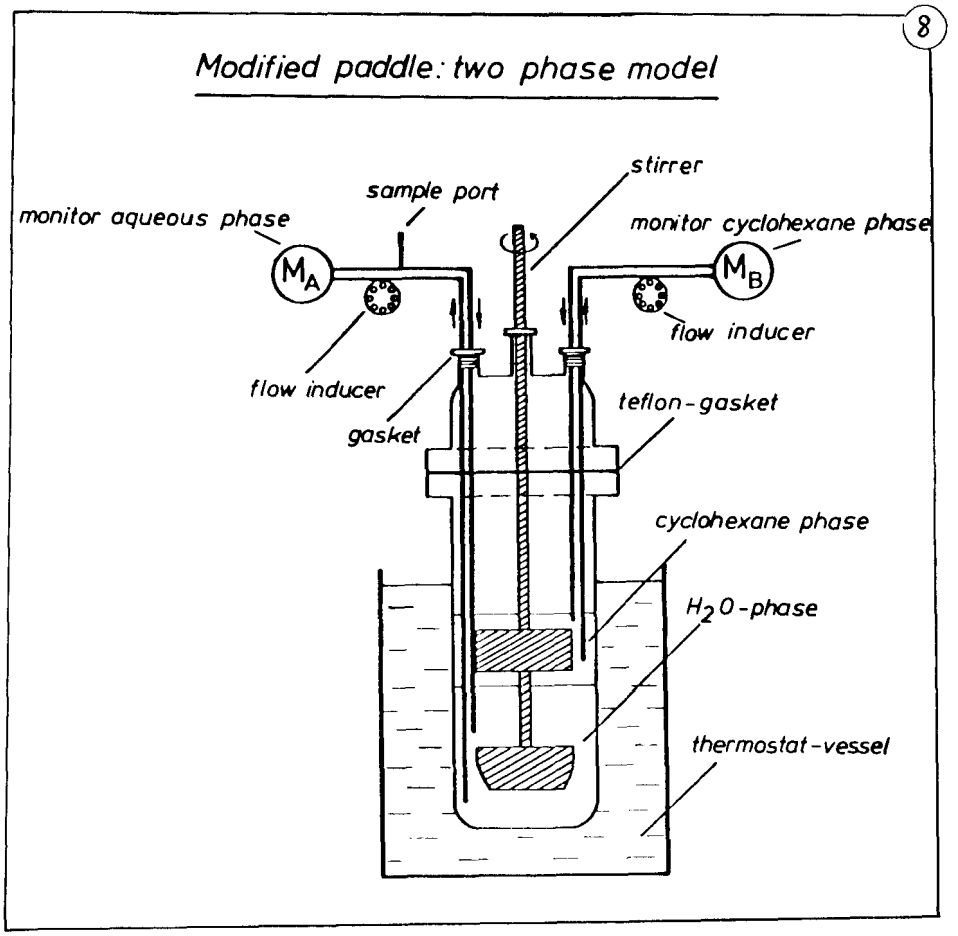


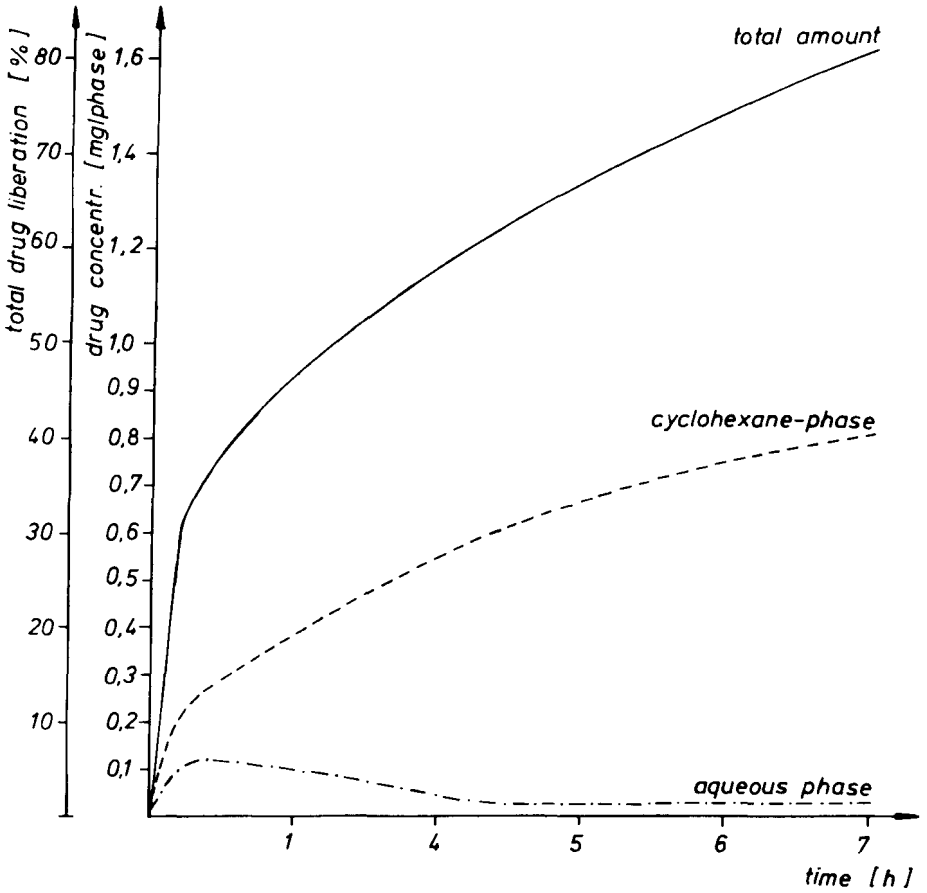
Figure 8

formed to a granulate mass, which is finally brought onto drying plates. After drying the material the desired particle size is obtained by crushing and sieving.

1.2.5. Production control

At the beginning of the polycondensation in substance or solution the polycondensation and drying process is easily monitored by measuring the viscosity of the batches. Subsequently the loss of weight is a useful parameter for batch control, based on the release of ethanol and, later in the process during the drying period, to the water desorption (fig. 4).

At this point it should be mentioned that codeine incorporated in PES acts as a moderate catalyst - (as "internal catalyst") - for the hydrolytic polycondensation of PES. Thus, the addition of ammonia is not necessary in this case.



In vitro drug liberation of papaverine from a SiO_2-embedding, using the modified paddle (two phases).

Figure 9

Catalytic properties are also shown by other drug bases (fig.5). Their catalytic activities vary over a broad scale and are dependent on the pK_b and the solubility of the bases in PES, as is seen from the table in fig. 6 : The rate of the increase of viscosity in the PES drug dispersions correlates with the solubility and the reciprocal of the pK_b of the bases in PES. Strong bases like ephedrine with low pK_b and high solubility are the most effective catalysts for polycondensation, increasing the viscosity of PES drug dispersions very rapidly.

2. Drug release from silica embedding

2.1. In vitro release experiments

Drug release properties of the silica-drug-embeddings were studied by several "in vitro" methods to minimize artefacts due to the in vitro release technique.

Factors influencing drug release from polycondensed PES envelopes

FACTOR	DRUG RELEASE RATE
External catalyst (NH_4)	increase
Increase of molecular weight of starting PES	decrease
Reduction of drug particle size	decrease
Increase of temperature during polymerisation	increase
Enlargment of the envelopes	decrease
Incorporation of water-soluble fillers	increase
Incorporation of insoluble fillers (fumed silica)	slight decrease

Figure 10

The USP paddle (9), a modified paddle with a cone-bottom vessel and a flow cell (10) were used in these experiments:

From molecular scale entrapments codeine is released with the same rate in the paddle apparatus and in the flow cell, while silica-codeine crystal embeddings obviously show a significant deviation in the USP paddle apparatus in comparison to the flow cell (fig.7).

Release tests with poorly soluble substances, such as papaverine base (at pH 7,4) were performed in a modified USP paddle device with cyclohexane as upper,

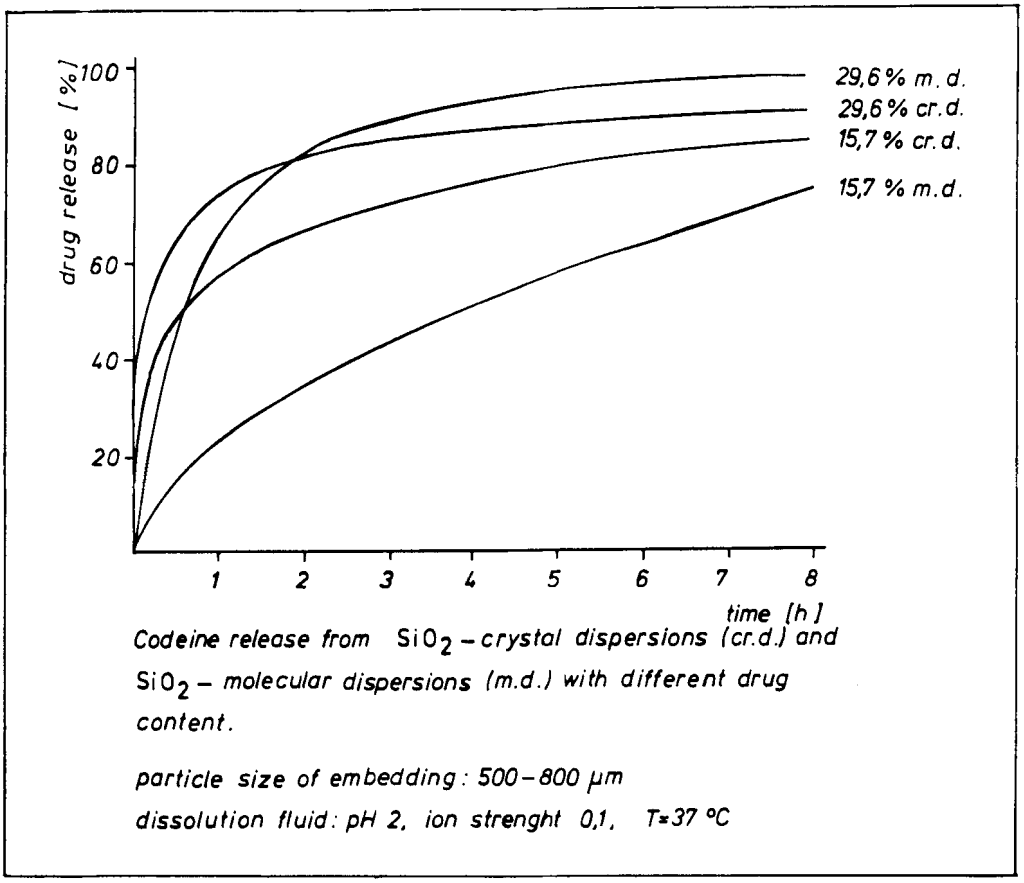


Figure 11

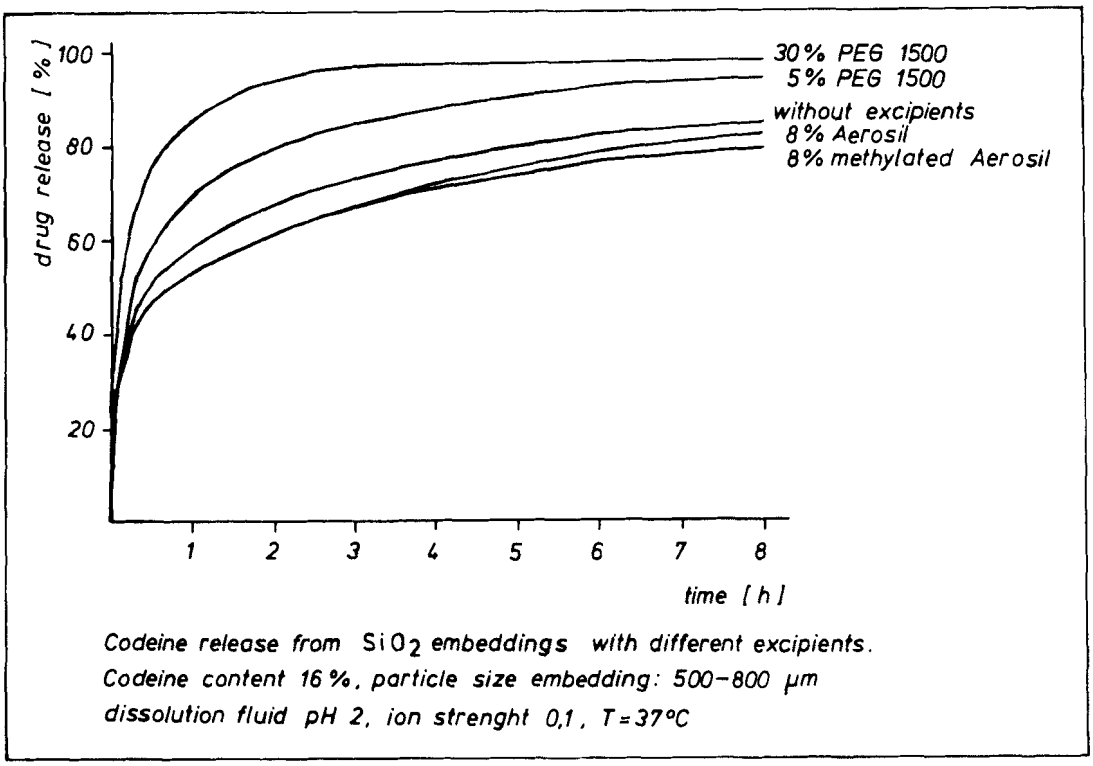
second phase (fig.8). With this device the drug liberation process can be monitored under pseudo-sink-conditions in the aqueous phase, if the partition coefficient cyclohexan/water is sufficient high. The time dependent amount of drug released was calculated from the sum of the amounts in the aqueous and the cyclohexane phase (fig. 9).

2.2. Influences on drug liberation from SiO_2 embeddings

Drug release from the polycondensed silica embedments depends on a series of parameters, concerning the composition of the drugs and the production conditions. These are outlined in tab.2 (fig.10) and some should be considered in detail:

2.2.1. Drug particle size and drug content

Drug particle size and drug content are dominant rate-determining parameters for drug release of basic drugs (such as codeine), incorporated in the SiO_2 matrix (fig.11):



Codeine release from SiO_2 embeddings with different excipients. Codeine content 16%, particle size embedding: 500–800 µm dissolution fluid pH 2, ion strenght 0,1, T=37°C

Figure 12

While from embedded crystals a more or less considerable amount of drug is initially liberated with a subsequent decreasing release - depending on both the particle size of the drug and the embeddings - the molecular entrapped codeine is released with an approximately constant initial rate, if the drug content is lower than 20%. On increasing the amount of codeine dissolved in PES the liberation rate exhibits a similar pattern to codeine crystal embeddings. This is obviously achieved by the stronger catalytic effect of higher amounts of dissolved base during the polycondensation process, leaving a porous silica matrix with larger pores.

2.2.2. Additives

It is well known that the liberation rate from drug envelopes with organic polymers can be influenced by the addition of soluble or insoluble substances into the wall material (11,12,13,14). From fig. 12 it becomes apparent that water soluble polymers such as polyethylene oxides enhance the liberation process, leaving obviously larger pores in the silica matrix after their dissolution in water. The incorporation of nonsoluble hydrophilic or hydrophobic fumed silicas into the PES only marginally effects the release rate of the drug.

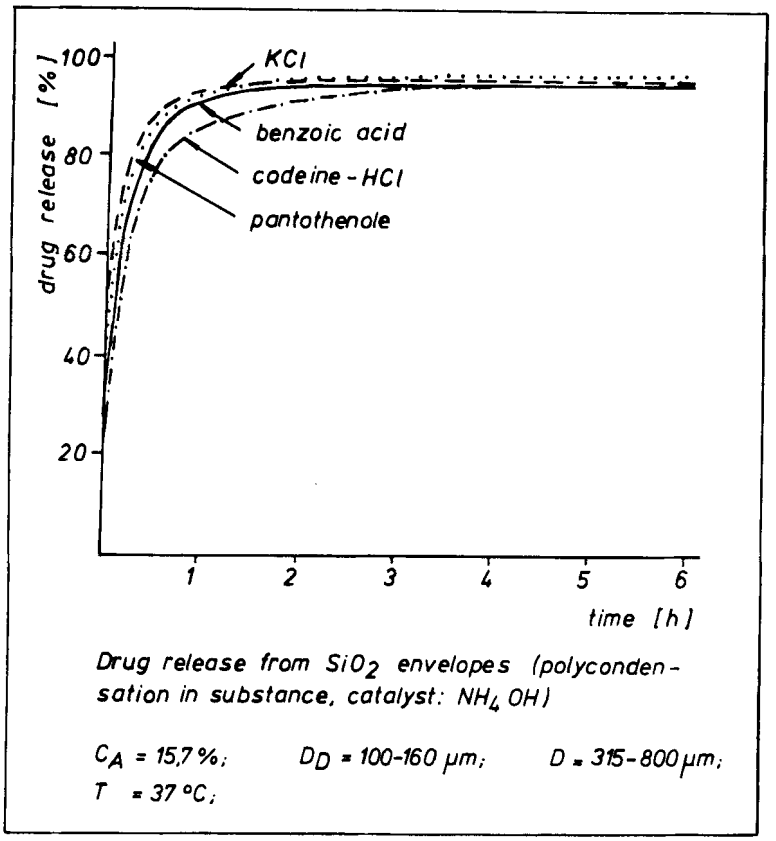


Figure 13

2.2.3. Drug liberation of nonionics, neutral salts and anionic drugs

Nonionic drugs like pantothenol, neutral salts like KCl, codeine-HCl or the anionic benzoic acid are very rapidly released from silica embeddings in comparison to the molecular entrapped drug bases (fig.13). This may be partly due to the larger pores, formed in the presence of ammonia as an "external" catalyst. The adsorption behaviour of the drugs on the silica matrix is another feature which must be taken into consideration: Only drug cations are absorbed appreciably to the negatively charged silica surface in aqueous dispersions (above all in neutral or alkaline media). Large hydrophobic moieties in the cations intensify their adsorption to the silica surface (15,16,17).

Thus embeddings of nonadsorbing substances (mentioned above) may be used for the separation of incompatible substances in drug preparations such as granulates, capsules, or tablets, if a spontaneous release is desired after contact with the gastro intestinal fluid.

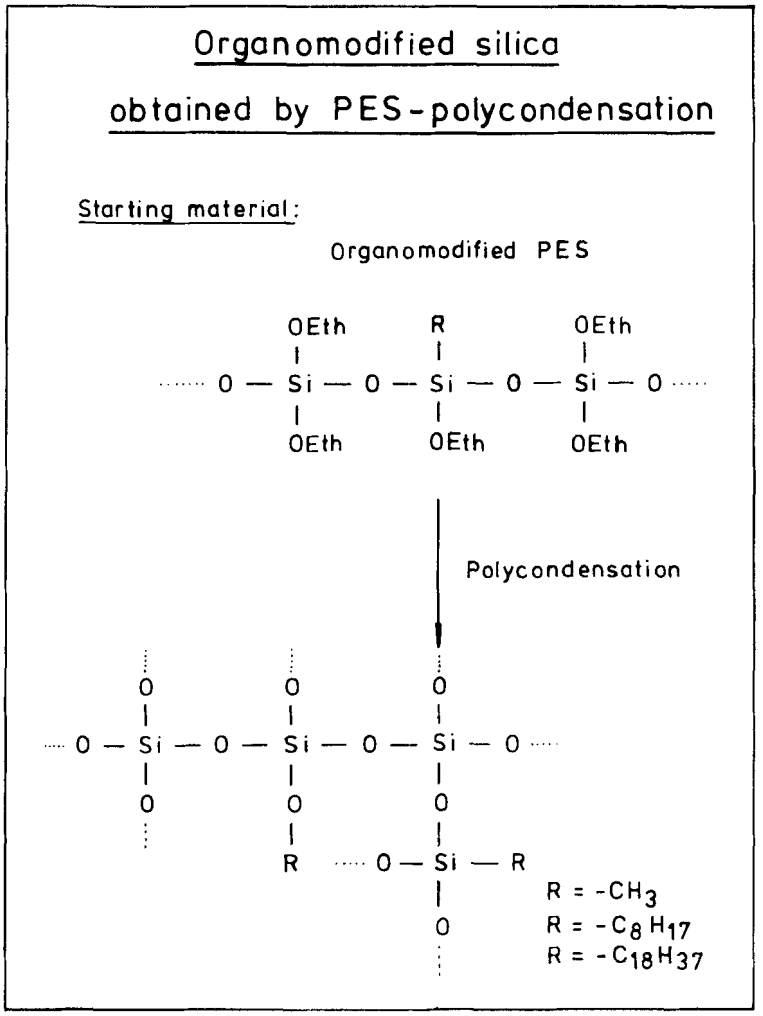


Figure 14

2.3. Organomodified PES

2.3.1. Structure

Hydrolytic polycondensation of PES also proceeds if some of the ethoxy groups in the starting PES material are substituted by organofunctional groups such as alkyl chains. These organic moieties are linked by the stable Si-C bond to the silicon backbone of the polymer (fig.14). The IR spectra of such hydrocarbon substituted PES are characterized by strong C-H valence bond absorptions. As an example the spectrum of a methylated PES is given in fig. 15 with absorption bands between 2850 cm^{-1}. The absorption band at 3630 cm^{-1} indicates the O-H valence bonds of free silanol groups in the polymer.

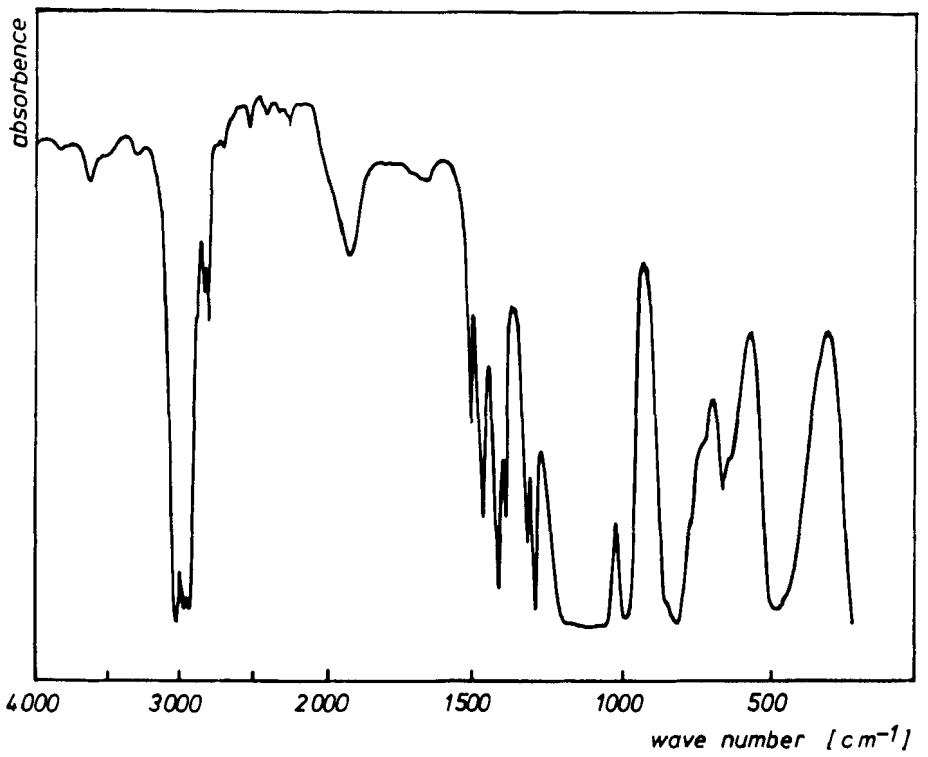


Figure 15

IR-spectrum of organo-modified polyethoxysiloxane *(methylated)*

2.3.2. Drug release

The hydrolytic polycondensation of drug dispersions in PES 350/alkyl-substituted PES-mixtures obviously yields drug embeddings with properties such as hydrophobic matrices. In comparison with the pure silica embeddings the release rate of molecular entrapped codeine is considerably reduced even at a low octyl-groups content of the matrix material (fig.16). Thus these mixtures can be used to close the gap between the pure hydrophilic silicas and the well known hydrophobic silicone polymer matrices on the field of controlled drug delivery.

2.4. Drug release from dosage forms

The silica embedded drugs can be incorporated easily into solid dosage forms like hard gelatine capsules or tablets. In the presence of a sufficient amount of tableting aids like Avicel, drug release is not significantly changed from tablets in comparison with the pure SiO_2 drug embedding, even in capsules (fig.17).

3. Organomodified fumed, nonporous silicas as stabilizer for suspensions

Organofunctional groups are introduced onto the surfaces of fumed silicas by chemisorption of organochlorosilanes at surface silanol groups. Being linked

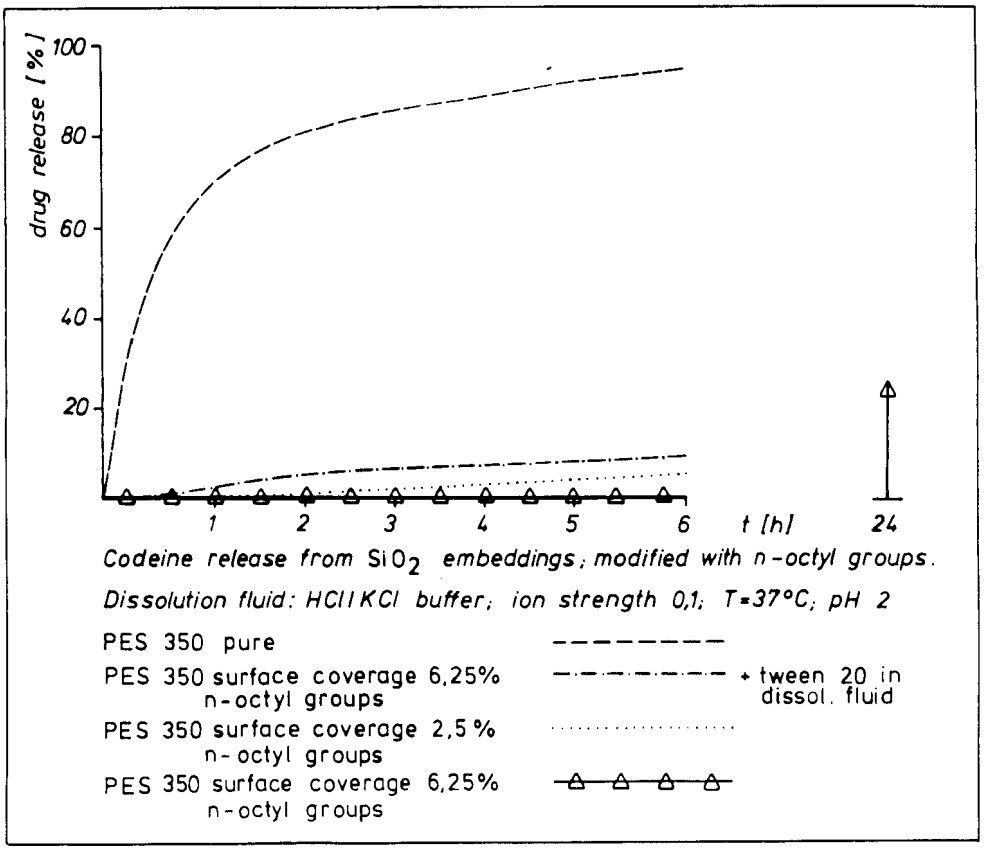


Figure 16

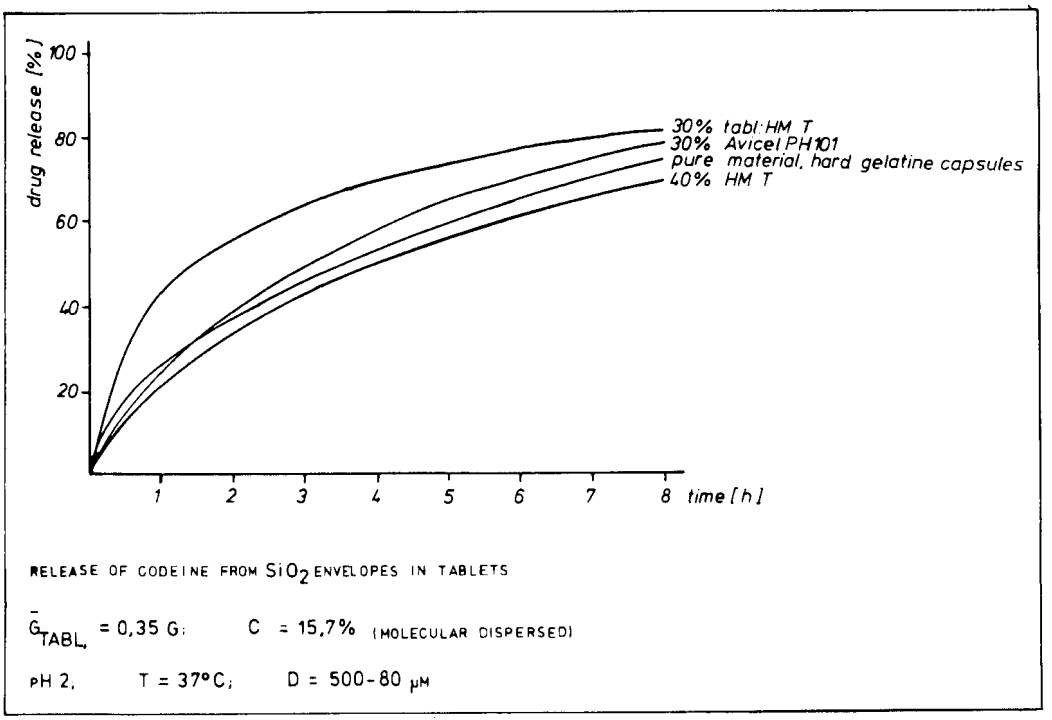


Figure 17

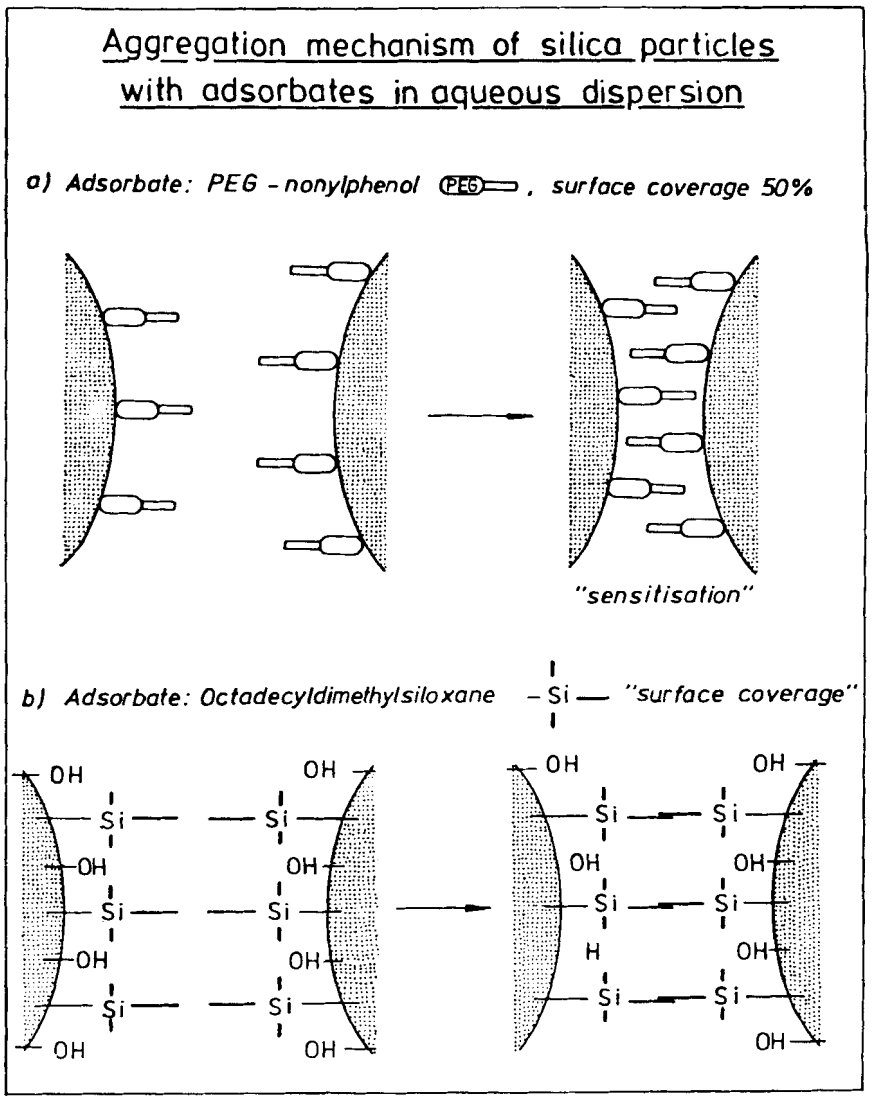


Figure 18

to the SiO_2 surface by stable Si-C-bonds, these render the surface of the silica particles more or less hydrophobic depending on the surface coverage of the chemisorbate.

It is well known from experiments with surface active substances, physisorbed onto colloidal silicas, that the corresponding aqueous dispersions show a remarkable aggregation of the silica within a narrow concentration of the surfactant. Under these conditions thixotropic gels are formed with silica concentrations higher than 4% (4,19). The contact between the silica particles

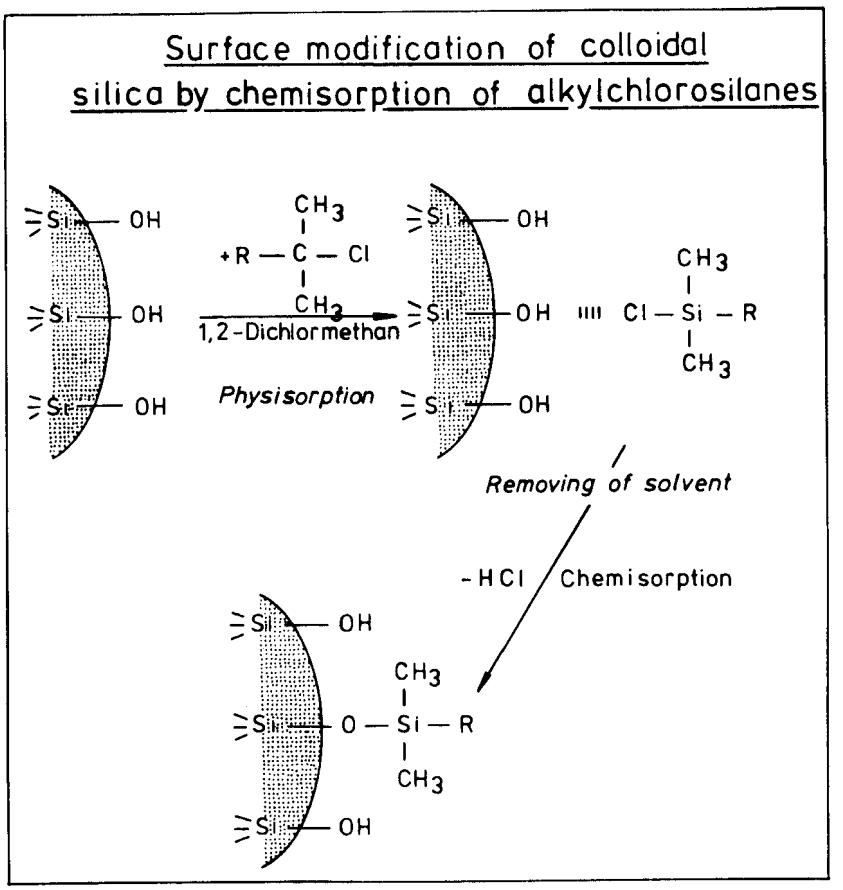


Figure 19

C-Analysis of chemisorbed octadecyldimethyl-groups on colloidal silica Aerosil

Surface coverage (%) (adjusted by adsorption equilibria)	*C content of adsorbates (%)*	*Surface coverage after chemisorption of octadecyldimethyl groups (%)*	*Surface density of adsorption* $\left(\frac{molecules}{nm^2}\right)$
8	2,84	8	0,36
13	3,28	10	0,41
20	5,40	17	0,68
30	8,50	27	1,07
40	11,29	35	1,41

Figure 20

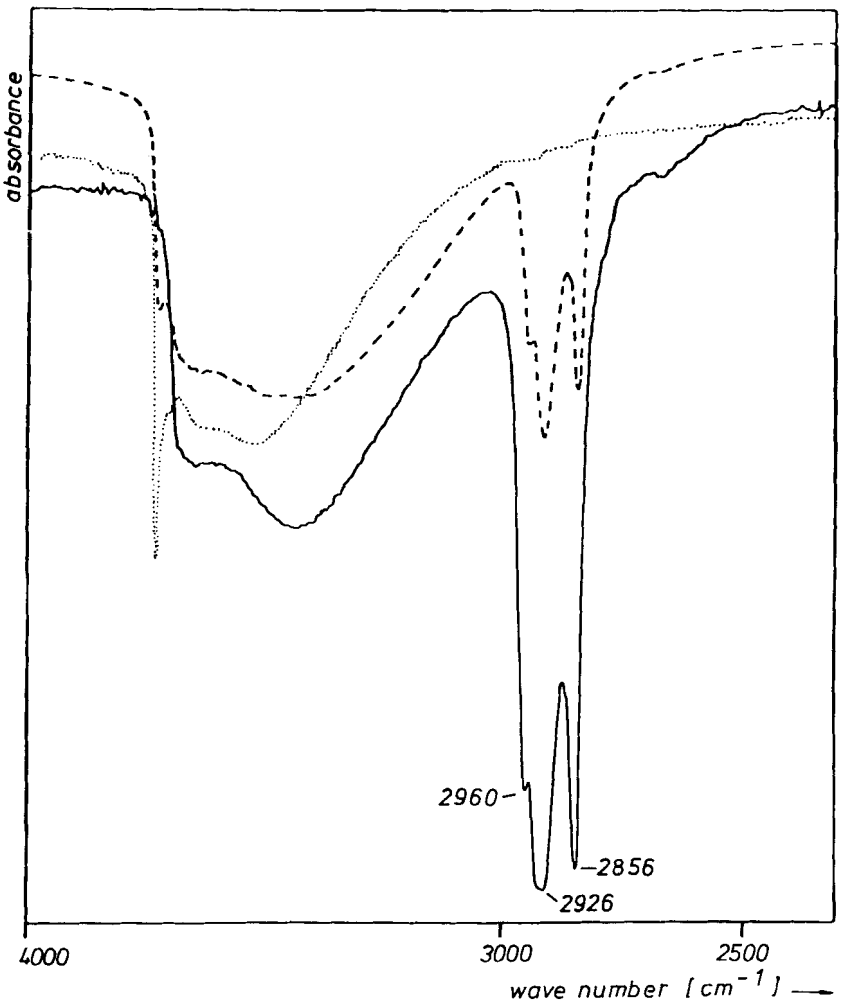


Figure 21

Chemisorbates of colloidal silica Aerosil and dimethyloctadecyl chlorosilane
surface coverage 20 % ————
8 % - - - - - - - -
pure silica surface .....

in these aggregates is established by hydrophobic interactions of the surfactant hydrocarbon chains, oriented perpendicularly to the surfaces (fig.13a). Naturally the adsorption of the surfactant and, therefore, the corresponding viscosity effects depend on a series of parameters such as additives, pH and temperature. They also influence the adsorption equilibria and, consequently, the mutual interactions between the particles.

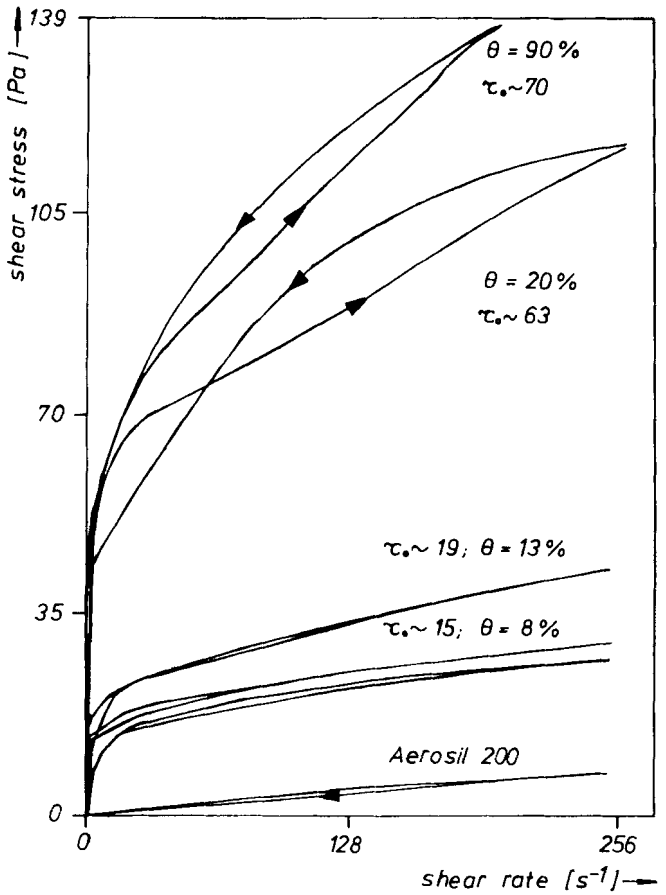


Figure 22

Viscosity of aqueous dispersions (5 %) of surface modified silica (Aerosil octadecyldimethylgroups). System: Rotovisco EMK 50 PK5

In view of these phenomena we had the idea to improve the gelling effect of the silica particle by chemisorption of surfactant-like moieties at the surface. A broad scale of surface coverage was investigated in order to evaluate the best conditions for the gelling or aggregating mechanism (fig.18b): First we physically adsorbed organochlorsilanes, like octadecyldimethylchlorosilane, onto the silica particles from a nonpolar solvent at a definite adsorption equilibrium. After removing the adsorbate from the liquid phase the chemisorption was followed by heating the adsorbates to the reaction temperature. (The reaction pathway is given schematically in fig.19).

The corresponding adsorbates are characterized by well defined surface coverage values (fig.20). IR-spectra of these adsorbates demonstrate the different

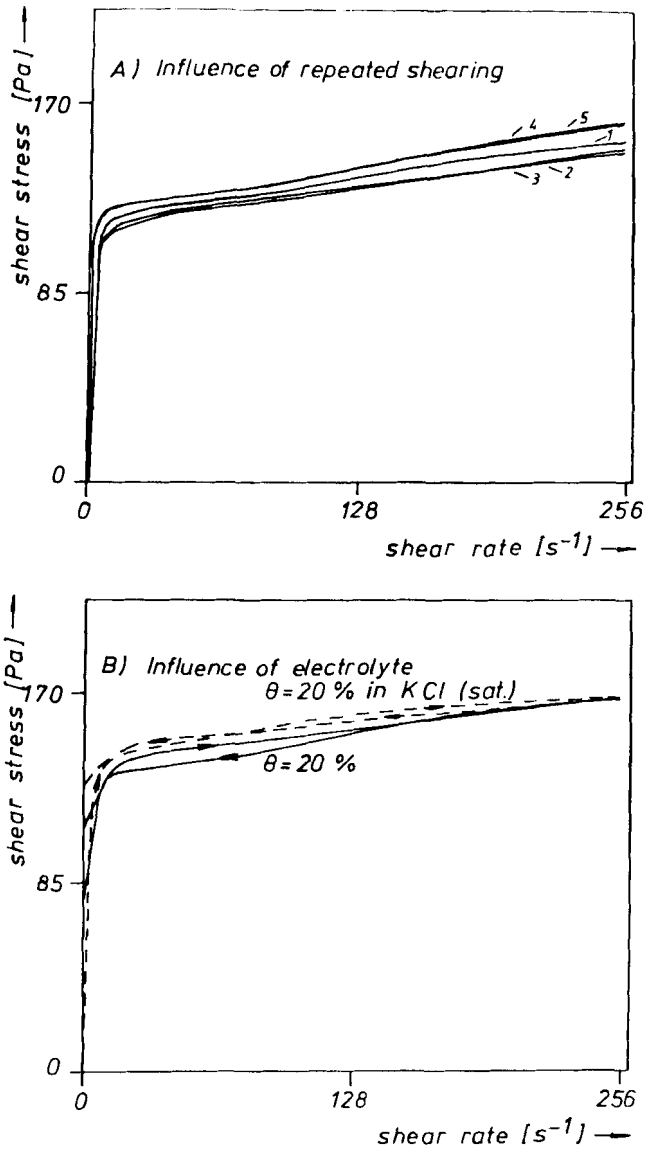


Figure 23

Viscosity of aqueous dispersions (5 %) of surface modified silica (Aerosil with octadecyl groups)under mechanical stress and in the presence of electrolytes.
System: Rotovisco EMK500 PK 5

degree of chemisorption as it is seen from the surface silanol absorption band at 3686 cm^{-1} and the CH-valence bands of the organic residue at 2960 cm^{-1} for the methyl-group and at 2856 cm^{-1} for the hydrocarbon chain, respectively (fig.21)[+].

These organomodified silicas form gels with plastic flow behaviour in aqueous dispersion at 5% silica content (fig.22). Starting with 8% organomodified groups on the silica particles, definite yield values are obtained.

Silicas with higher adsorption densities of organofunctional groups achieve a remarkable increase of the yield value and a typical dilatant flow behaviour at higher shear rates. This may be due to a stiff network of aggregated silica, in which the single silica particles are stack together by the hydrophobic chemisorbate, forming strings of beads (20). In contrast pure Aerosil dispersions show no yield value even at 10% silica in aqueous dispersions.

These gels are very insensitive with respect to the addition of neutral salts like KCl or to a repeated mechanical stress (fig.23). From this we can state that the surface modified silicas can be used as gelling and thickening agents similar to swelling clays without the great number of incompatibilities of the clays with respect to ion exchange and intercalation.

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