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Contact angles of surfactants with a potential to alter the body distribution of colloidal drug carriers on poly(methyl methacrylate) surfaces

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Summary

Advancing and receding contact angles of various aqueous surfactant solutions were measured on poly(methyl methacrylate) surfaces and the hysteresis vs surfactant concentration areas were determined. Plots of adhesion tension, $\gamma_{LV} \cos \theta$, vs surface tension γ_{LV} were also used to determine the affinity of the surfactants to the polymer surface. The surfactants were classified into 4 groups according to the above characteristics. The classification was compared to body distribution data taken from the literature of surfactant-coated nanoparticles after i.v. injection.

Introduction

The uptake of colloidal drug carriers (< 1000 nm) by the macrophages of the reticuloendothelial system (RES), especially in the liver and the spleen, after i.v. administration (Juhlin, 1960; Kreuter et al., 1979; Grislain et al., 1983; Leu et al., 1984; Davis and Illum, 1986; Illum et al., 1987; Waser et al., 1987) is a major obstacle for the targeting of these carriers to other parts of the body. As shown previously (Wilkins, 1966; Wilkins and Myers, 1966; Scott et al., 1967; Illum et al., 1982, 1986; Douglas et al., 1985), the distribution pattern of colloidal particles mainly depends on their size, their surface charge and their surface properties. Therefore it should be possible to change the body distribution by coating the particles with surfactants: Illum et al., 1982, 1986, 1987; Leu et al., 1984; Douglas et al., 1985; and Davis and Illum, 1986 demonstrated a reduction in liver uptake of nanoparticles by this method. The purpose of the present investigation is to classify the surfactants by an in-vitro method and possibly find new surfactants with more effective targeting properties.

One of the possible methods for the in-vitro determination of the surface properties is the measurement of contact angles of the surfactant solutions on the polymer material. The contact angle is an expression of the interaction of the surfactant with the nanoparticle material and consequently its ability to change the surface character-

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istics of the nanoparticles (Andrade et al., 1979; Coleman et al., 1982; Kreuter, 1983; Hogt et al., 1985; Murray, 1986; Johnson, 1985; Johnson et al., 1986; Zografi and Johnson, 1984). Poly(methyl methacrylate) (PMMA) was chosen as the model polymer carrier material, because it is of intermediate lipophilicity, can be ^{14}C-labeled within the polymer chain, and is only very slowly biodegradable. The latter properties enable an accurate determination of the body distribution of virtually undegraded carriers within 1 week.

Materials and Methods

Surfactants

The poloxamers and poloxamines were obtained from C.H. Erbslöh (Düsseldorf-Hafen, F.R.G.), the polysorbates and sorbitan fatty acid esters from Atlas-Chemie (Essen, F.R.G.), polyoxyethylene(23)laurylether from Fluka AG (Chem. Fabrik, Buchs, Switzerland), Triton X-100 from Sigma Chemical Company (St. Louis, U.S.A.), sodium di(2-ethylhexyl)sulfosuccinate (AOT) from Merck (Darmstadt, F.R.G.) and Genapol PF 10 from Hoechst AG (Frankfurt, F.R.G.).

Bovine serum

Bovine serum was obtained from Behring Institute (Normalserum vom Rind; Marburg, F.R.G.), stored frozen in portions of 3–4 ml at -18 to $-20\,^{\circ}C$ and used only at the day of thawing.

PMMA plates

PMMA plates (Plexiglas^{R}, gs farblos 233) were obtained from Röhm Pharma (Darmstadt, F.R.G.) and cut into sheets of a size of 10 cm × 4 cm × 0.3 cm. They were cleaned with a 1% aqueous polysorbate 20 (Tween^{R} 20) solution rinsed with normal water, then with demineralized water and finally dried with a lint-free tissue. The cleaned plates were stored in a desiccator.

Contact angle measurements

A modified version of the chamber described by Johnson (1982) and Johnson et al. (1986) consisting of an air-tight Plexiglas box of inner dimensions 21 × 9.5 × 16 cm was built to allow control of the environment surrounding a drop during contact angle measurement. Several beakers filled with test liquid were placed inside the chamber to maintain a saturated atmosphere and to retard evaporation. The temperature inside the chamber very near the drop was maintained at $25 \pm 1.0\,^{\circ}C$ by circulating water through copper tubing. Details of the apparatus are described elsewhere (Johnson, 1982). A known volume of the test liquid was either added or removed using an assembly consisting of a syringe (gas-tight Luer-lock syringe, Hamilton Co.) fitted to a Steinmeyer micrometer head and holder (Desaga, Heidelberg, F.R.G.). Advancing and receding contact angles on the same drop were measured by keeping the needle in contact with the drop throughout the experiment while adding and removing liquid. The sessile drop was viewed through a glass window using a goniometer telescope (Leitz, Wetzlar, F.R.G.), and contact angles were read directly to the nearest $1.0\,^{\circ}$ from each side of the drop. 30 min were required for the surfactant solutions to reach equilibrium.

Surface tension

The surface tension of all pure liquids and solutions was measured at $25 \pm 1.0\,^{\circ}C$ using the Lecomte Du Noüy-ring method (MGW-Lauda-Tensiometer, Lauda, F.R.G.). Up to as much as 30 min were required to attain equilibrium values. The S.D. for the surface tension values of the surfactant solutions was generally less than 0.5 mN/m^{-1}.

Coating experiments

The cleaned PMMA plates were placed in the 1% surfactant solutions for 30 min. The samples were then shaken dry and placed horizontally in a desiccator at $60\,^{\circ}C$ for about 15 h. The contact angles of phosphate-buffered saline as well as of bovine serum were then determined on these surfactant coated plates. The results are shown in Tables 4 and 5.

Results

Contact angles and surface tensions of surfactant solutions

The water contact angles on PMMA were determined as a reference for the data obtained with the surfactant solutions. Angles of 77° were obtained for the advancing angle θ_A and 61° for the receding angle θ_R. From the advancing and receding contact angles the hysteresis H can be calculated using Eqn. 1:

$$H = \theta_A - \theta_R \quad (1)$$

In the case of water, the hysteresis was found to be 16°.

In Table 1 the contact angles and hysteresis values of the surfactant solutions are listed. After plotting the contact angles vs the surfactant concentrations, it was possible to classify the surfactants into 4 groups (Table 2). Examples of plots of typical representatives of these groups are shown in Figs. 1–4. The characteristics of these groups are listed in Table 3.

Contact angles on surfactant coated PMMA plates

The contact angles of phosphate-buffered saline and bovine serum on PMMA plates after coating with surfactant solutions are shown in Tables 4 and 5. The S.D.s were higher than with those of the surfactant solutions on clean PMMA surfaces. The reason for this is probably due to uneven coating of the samples.

It is interesting to note that the contact angles of bovine serum albumin were equal or slightly higher than with phosphate-buffered saline. With

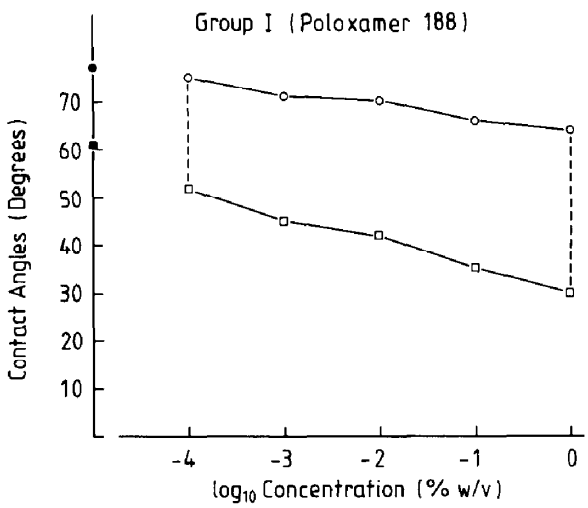

Fig. 1. Contact angle hysteresis vs concentration of poloxamer 188 (Group I). ○, Advancing contact angles; □, receding contact angles; ●, water advancing contact angle; ■, water receding contact angle.

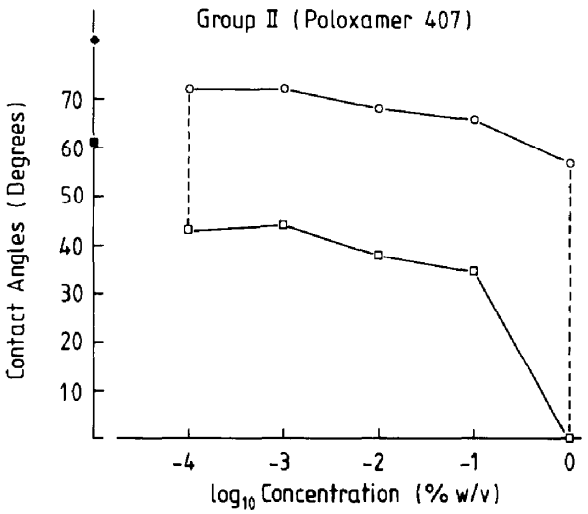

Fig. 2. Contact angle hysteresis vs concentration of poloxamer 407 (Group II). Symbols as in Fig. 1.

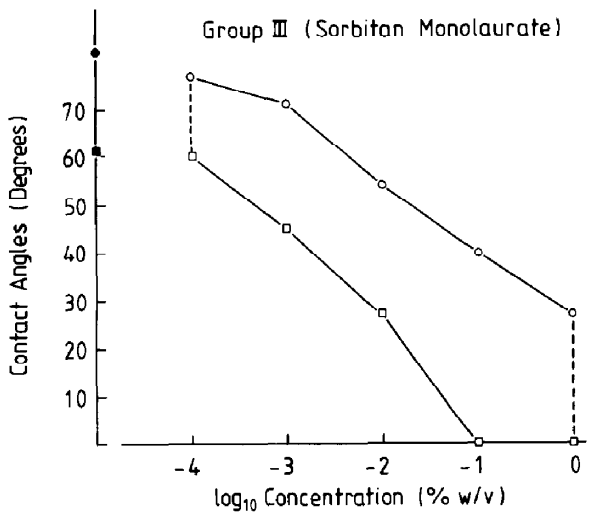

Fig. 3. Contact angle hysteresis vs concentration of sorbitan monolaurate (Group III). Symbols as in Fig. 1.

TABLE 1

Contact angles ± S.D. of surfactants on PMMA at 25 °C

Concentration (% w/v)	γ_{LV} (mN/m)	θ_A	θ_R	H
Polysorbate 20 (Tween 20)				
10^{-4}	60.1	79° ±3	58° ±3	21°
10^{-3}	42.6	72° ±3	45° ±5	27°
10^{-2}	37.0	51° ±2	22° ±1	29°
10^{-1}	34.7	44° ±3	0° ±0	44°
10°	33.6	37° ±2	0° ±0	37°
Polysorbate 60 (Tween 60)				
10^{-4}	56.2	77° ±1	56° ±2	21°
10^{-3}	42.2	71° ±2	38° ±2	33°
10^{-2}	38.3	64° ±1	31° ±1	33°
10^{-1}	37.1	60° ±2	29° ±1	31°
10°	35.7	57° ±1	28° ±1	29°
Polysorbate 80 (Tween 80)				
10^{-4}	61.6	77° ±2	57° ±7	20°
10^{-3}	49.1	74° ±2	39° ±3	35°
10^{-2}	42.7	61° ±3	29° ±3	32°
10^{-1}	39.0	58° ±2	26° ±2	32°
10°	36.1	50° ±2	0° ±0	50°
Polysorbate 85 (Tween 85)				
10^{-4}	55.6	78° ±1	61° ±1	17°
10^{-3}	49.5	72° ±3	47° ±5	25°
10^{-2}	43.6	60° ±2	31° ±1	29°
10^{-1}	34.4	49° ±3	23° ±5	26°
10°	33.4	43° ±5	0° ±0	43°
Sorbitan monolaurate (Span 20)				
10^{-4}	67.6	77° ±3	60° ±1	17°
10^{-3}	43.6	71° ±1	45° ±1	26°
10^{-2}	30.2	54° ±2	27° ±2	27°
10^{-1}	26.4	40° ±2	0° ±0	40°
10°	25.4	27° ±2	0° ±0	27°
Sorbitan monopalmitate (Span 40)				
10^{-4}	52.7	78° ±2	59° ±1	19°
10^{-3}	42.4	78° ±1	46° ±2	32°
10^{-2}	40.8	75° ±2	36° ±3	39°
10^{-1}	44.2	66° ±5	31° ±5	35°
10°	47.9	61° ±2	32° ±2	29°
Sorbitan monostearate (Span 60)				
10^{-4}	72.5	80° ±2	61° ±2	19°
10^{-3}	55.0	79° ±1	51° ±2	28°
10^{-2}	46.4	73° ±1	40° ±1	33°
10^{-1}	47.8	70° ±2	39° ±2	31°
10°	56.9	72° ±2	41° ±2	31°
Sorbitan mono-oleate (Span 80)				
10^{-4}	30.2	77° ±2	56° ±2	21°
10^{-3}	29.6	72° ±1	42° ±4	30°
10^{-2}	29.4	56° ±2	31° ±1	25°
10^{-1}	28.7	43° ±2	0° ±0	43°
10°	29.5	37° ±4	0° ±0	37°

TABLE 1 (continued)

Concentration (% w/v)	γ_{LV} (mN/m)	θ_A	θ_R	H
Sorbitan Trioleate (Span 85)				
10^{-4}	59.6	76° ±3	56° ±2	20°
10^{-3}	42.3	75° ±2	48° ±4	27°
10^{-2}	36.7	71° ±2	45° ±2	26°
10^{-1}	32.4	62° ±1	45° ±2	17°
10°	31.5	53° ±2	29° ±2	24°
Poloxamine 304				
10^{-4}	56.8	72° ±2	47° ±1	25°
10^{-3}	59.0	70° ±2	46° ±4	24°
10^{-2}	50.2	62° ±3	48° ±2	14°
10^{-1}	45.5	61° ±2	40° ±4	21°
10°	41.9	51° ±4	26° ±5	25°
Poloxamine 904				
10^{-4}	47.0	72° ±1	34° ±3	38°
10^{-3}	42.5	61° ±2	26° ±2	35°
10^{-2}	37.8	48° ±1	0° ±0	48°
10^{-1}	34.2	34° ±5	0° ±0	34°
10°	34.1	25° ±2	0° ±0	25°
Poloxamine 908				
10^{-4}	60.8	75° ±2	49° ±1	26°
10^{-3}	53.1	70° ±2	37° ±6	33°
10^{-2}	47.1	65° ±2	0° ±0	65°
10^{-1}	42.4	58° ±2	0° ±0	58°
10°	37.0	51° ±2	0° ±0	51°
Poloxamine 1508				
10^{-4}	62.0	73° ±2	41° ±1	32°
10^{-3}	44.2	69° ±2	29° ±2	40°
10^{-2}	44.4	64° ±2	0° ±0	64°
10^{-1}	41.9	59° ±2	0° ±0	59°
10°	38.6	51° ±2	0° ±0	51°
Poloxamer 108				
10^{-4}	60.1	77° ±2	57° ±2	20°
10^{-3}	56.8	74° ±2	52° ±2	22°
10^{-2}	49.7	72° ±2	53° ±2	19°
10^{-1}	46.3	67° ±1	40° ±1	27°
10°	40.5	62° ±1	30° ±3	32°
Poloxamer 184				
10^{-4}	51.5	76° ±2	55° ±2	21°
10^{-3}	46.9	70° ±2	45° ±3	25°
10^{-2}	38.3	64° ±1	35° ±3	29°
10^{-1}	31.2	39° ±1	0° ±0	39°
10°	29.3	14° ±4	0° ±0	14°
Poloxamer 188				
10^{-4}	57.1	75° ±1	52° ±3	23°
10^{-3}	56.4	71° ±1	45° ±3	26°
10^{-2}	52.8	70° ±2	42° ±1	28°
10^{-1}	49.5	66° ±1	35° ±1	31°
10°	46.5	64° ±3	30° ±5	34°
Poloxamer 338				
10^{-4}	60.0	76° ±3	57° ±3	19°
10^{-3}	48.5	74° ±2	40° ±4	34°
10^{-2}	42.8	60° ±3	28° ±6	32°
10^{-1}	39.2	55° ±1	0° ±0	55°
10°	37.7	52° ±2	0° ±0	52°

TABLE 1 (continued)

Concentration (% w/v)	γ_{LV} (mN/m)	θ_A	θ_R	H
Poloxamer 407				
10^{-4}	57.1	72° ±2	43° ±3	29°
10^{-3}	54.1	72° ±3	44° ±1	28°
10^{-2}	51.2	68° ±1	38° ±2	30°
10^{-1}	42.9	66° ±1	35° ±2	31°
10°	40.3	57° ±1	0° ±0	57°
Polyoxyethylene(23) laurylether (Brij 35)				
10^{-4}	47.1	71° ±2	41° ±4	30°
10^{-3}	43.3	66° ±2	28° ±7	38°
10^{-2}	36.3	54° ±2	0° ±0	54°
10^{-1}	42.8	51° ±3	0° ±0	51°
10°	43.9	48° ±2	0° ±0	48°
Sodium di(2-ethylhexyl)sulfosuccinate (Aerosol OT)				
10^{-4}	66.7	75° ±3	62° ±2	13°
10^{-3}	57.5	74° ±2	52° ±2	22°
10^{-2}	46.8	71° ±2	45° ±3	26°
10^{-1}	28.2	34° ±6	0° ±0	34°
10°	25.2	0° ±0	0° ±0	0°
Genapol PF 10				
10^{-4}	50.2	69° ±3	52° ±4	17°
10^{-3}	45.9	64° ±1	49° ±2	15°
10^{-2}	42.0	57° ±3	42° ±4	15°
10^{-1}	38.6	49° ±2	36° ±3	13°
10°	33.3	31° ±2	0° ±0	31°
Triton^R X-100				
10^{-4}	61.9	73° ±2	52° ±3	21°
10^{-3}	51.8	65° ±2	33° ±3	32°
10^{-2}	30.2	31° ±4	0° ±0	31°
10^{-1}	30.3	17° ±4	0° ±0	17°
10°	30.5	12° ±3	0° ±0	12°

phosphate-buffered saline, receding contact angles above zero were only observed in group I with one additional exception in group II (Genapol). The hysteresis values in groups II–IV were very small, never exceeding 15°.

With bovine serum, only Group IV showed consistent zero receding contact angles and small hysteresis values. In the other groups, the contact angle pattern was more complex, again with generally the highest advancing and receding angles in Group I.

Discussion

Advancing and receding contact angles are an expression of the interaction of the surfactant with liquid or solid surfaces. Especially the receding angles are influenced greatly by the affinity of the surfactant to the solid. Consequently, surface-active substances with a strong interaction and adherence to the solid should be characterized by a low receding angle and a large hysteresis area. For this reason, the surfactants investigated in this study were classified according to the criteria listed in Table 3, where Group I should have the lowest affinity and Group IV the strongest affinity to the solid surface.

Another possibility of analyzing contact angle data is the plot of adhesion tension, $\gamma_{LV} \cos \theta$, vs surface tension, γ_{LV} (Johnson et al., 1986). Using the expression developed by Lucassen-Reynders (1963) shown in Eqn. 2,

$$\frac{d(\gamma_{LV} \cos \theta)}{d\gamma_{LV}} = \frac{\Gamma_{SV} - \Gamma_{SL}}{\Gamma_{LV}} \quad (2)$$

(L, liquid; S, solid; V, vapor) where Γ_{SV}, Γ_{LV} and Γ_{SL} are the amounts adsorbed per unit area at each interface and assuming Γ_{SV} to be equal to

TABLE 2

Classification of the surfactants according to the criteria listed in Table 3

Group I	Group II	Group III	Group IV
Sorbitan monostearate	Poloxamer 407	Sodium di(2-ethylhexyl)sulfosuccinate	Poloxamine 904
Poloxamer 188	Polysorbate 80	Poloxamer 184	Poloxamer 338
Polysorbate 60	Polysorbate 85	Sorbitan monolaurate	Polyoxyethylene(23)laurylether
Sorbitan monopalmitate	Genapol PF 10	Sorbitan mono-oleate	Poloxamine 908
Poloxamine 304		Polysorbate 20	Poloxamine 1508
Sorbitan trioleate		Triton X-100	
Poloxamer 108			

TABLE 3

Characteristics of the surfactant groups

Group I	Group II	Group III	Group IV
High advancing angles	medium advancing angles	low advancing angles	high advancing angles
High receding angles	medium receding angles	low receding angles	very low receding angles
Small hysteresis area	medium hysteresis area	medium hysteresis area	large hysteresis area

TABLE 4

Contact angles of phosphate-buffered saline and bovine serum on PMMA plates after coating with a 1% (w/v) surfactant solution and subsequent drying

Surfactant	Phosphate buffered saline			Bovine serum		
	θ_A	θ_R	H	θ_A	θ_R	H
Polysorbate 20	0° ± 0	0° ± 0	0°	1° ± 2	0° ± 0	1°
Polysorbate 60	0° ± 0	0° ± 0	0°	4° ± 4	0° ± 0	4°
Polysorbate 80	0° ± 0	0° ± 0	0°	7° ± 2	0° ± 0	7°
Polysorbate 85	4° ± 6	0° ± 0	4°	17° ± 3	0° ± 0	17°
Sorbitan monolaurate	5° ± 3	0° ± 0	5°	2° ± 5	0° ± 0	2°
Sorbitan monopalmitate	19° ± 4	1° ± 4	18°	22° ± 5	0° ± 0	22°
Sorbitan monostearate	26° ± 17	0° ± 0	26°	54° ± 9	26° ± 4	28°
Sorbitan Mono-oleate	14° ± 3	0° ± 0	14°	18° ± 7	0° ± 0	18°
Sorbitan trioleate	22° ± 2	21° ± 1	1°	21° ± 7	0° ± 0	21°
Polyoxyethylene(23)laurylether	0° ± 0	0° ± 0	0°	14° ± 2	0° ± 0	14°
Genapol PF 10	27° ± 16	14° ± 14	13°	41° ± 6	22° ± 2	19°
Triton X-100	0° ± 0	0° ± 0	0°	16° ± 7	0° ± 0	16°
Sodium di(2-ethylhexyl)sulfosuccinate	0° ± 0	0° ± 0	0°	39° ± 5	18° ± 3	21°
Poloxamine 304	41° ± 24	8° ± 15	33°	39° ± 23	12° ± 13	27°
Poloxamine 904	0° ± 0	0° ± 0	0°	6° ± 5	0° ± 0	6°
Poloxamine 908	15° ± 4	0° ± 0	15°	13° ± 10	0° ± 0	13°
Poloxamine 1508	15° ± 6	0° ± 0	15°	13° ± 5	0° ± 0	13°
Poloxamer 108	2° ± 4	0° ± 0	2°	17° ± 5	0° ± 0	17°
Poloxamer 184	12° ± 12	0° ± 0	12°	32° ± 9	20° ± 3	12°
Poloxamer 188	32° ± 27	17° ± 17	15°	64° ± 3	30° ± 8	34°
Poloxamer 338	3° ± 4	0° ± 0	3°	5° ± 3	0° ± 0	5°
Poloxamer 407	0° ± 0	0° ± 0	0°	1° ± 2	0° ± 0	1°
PMMA without coating	69° ± 3	31° ± 6	38°	60° ± 3	29° ± 1	31°

TABLE 5

Organ uptake of nanoparticles after coating with different surfactants (literature values)

Surfactant	Literature	Liver uptake (%)		Liver uptake reduction (%)	Spleen uptake (%)		Bone marrow uptake (%)	Time (days)
		Without coating	With coating		Without coating	With coating		
Poloxamer 188 (Group I)	A	74	51	31	5	23	n.d.	7
Poloxamer 407 (Group II)	B	57	8	86	n.d.	n.d.	70	8
Poloxamer 338 (Group IV)	C	60	30	49	1.5	1.0	n.d.	8
Poloxamine 908 (Group IV)	C	60	19	68	1.5	1.2	n.d.	8

Literature: A, Leu et al., 1984; B, Davis and Illum, 1986; C, Illum et al., 1987; n.d. = not determined.

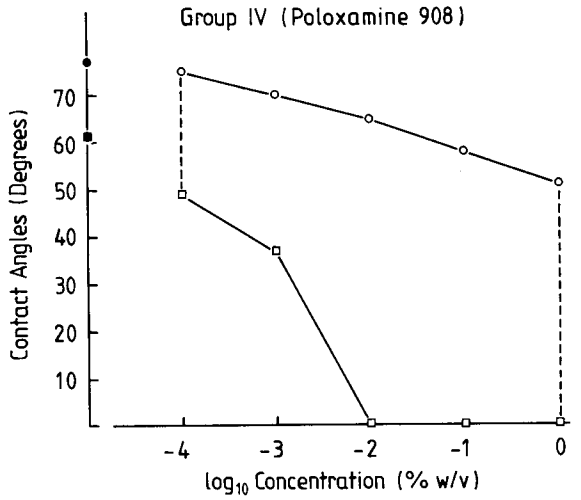

Fig. 4. Contact angle hysteresis vs concentration of poloxamine 908 (Group IV). Symbols as in Fig. 1.

zero, it can be shown, as in Fig. 5, how the ratio of adsorption at each interface can affect wettability (Johnson et al., 1986). The assumption of Γ_{SV} to be equal to zero is reasonable for a low energy solid such as PMMA. A slope of cosine $\theta = 1$ is the limiting line obtained for complete wetting. The other two extremes occur when there is much more adsorption to the liquid–vapor interface so

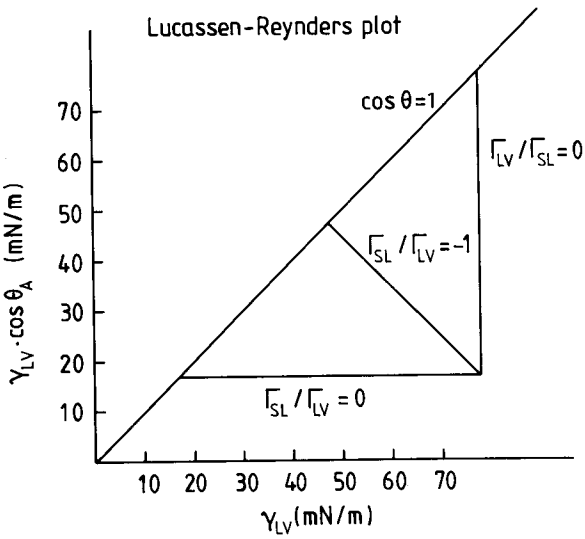

Fig. 5. Theoretical adhesion tension, $\gamma_{LV} \cos \theta$, vs surface tension, γ_{LV}, plots for surface-active solutions assuming Γ_{SL}/Γ_{LV} equal to zero, one or infinity.

that the ratio of the surface excess Γ_{SV}/Γ_{LV} is equal to zero and the data appear as a horizontal line (Johnson, 1982). Conversely, if there is much more adsorption to the solid–liquid interface than to the liquid–vapor interface, the ratio of Γ_{SL}/Γ_{SV} goes to infinity and the slope appears as a vertical line. Equal adsorption to the solid–liquid and liquid–vapor interface is characterized by a slope of -1.

In the Lucassen-Reynders plot at a given concentration (e.g. 10^{-1}% (w/v), Fig. 6) the surfactants belonging to each of the 4 different classifications appear closely grouped together. All surfactants show a tendency for a stronger adsorption to the liquid–vapor than to the solid–liquid interphase. This behaviour is especially pronounced in Group I, followed by Group II.

When the Lucassen-Reynders plot is carried out at different concentrations of the surfactants, again differences between the 4 surfactant groups can be observed. Typical examples of representatives of the four surfactant groups are shown in Fig. 7. The decrease of the adhesion tension $\gamma_{LV} \cos \theta$ of some surfactant solutions to below the water value, which should not be possible according to the theory assuming Γ_{SV} to be approximately zero (Eqn. 2), is probably caused by uncertainties in the contact angle measurements. As shown by Johnson (1982) and also observed in this study, the accuracy of the contact angle measurement lies at 1°–3°. At angles around 77° (water value) an alteration by only 1° decreases or increases $\cos \theta_A$ and consequently $\gamma_{LV} \cos \theta_A$ by about 10%.

At concentrations below 10^{-4}% (w/v), all surfactants undergo a very small influence of the variation of the concentration on the contact angle but a somewhat greater effect on the surface tension. This demonstrates that the surfactants adsorb preferentially to the liquid–vapor surface at these concentrations. At higher concentrations, the Lucassen-Reynders plot shows that the affinity of the surfactants to the liquid–solid surface increases in the order Group I < Group II < Group III < Group IV.

The high affinity of the Group IV surfactants to the PMMA is also demonstrated by the low advancing and consistently zero receding contact

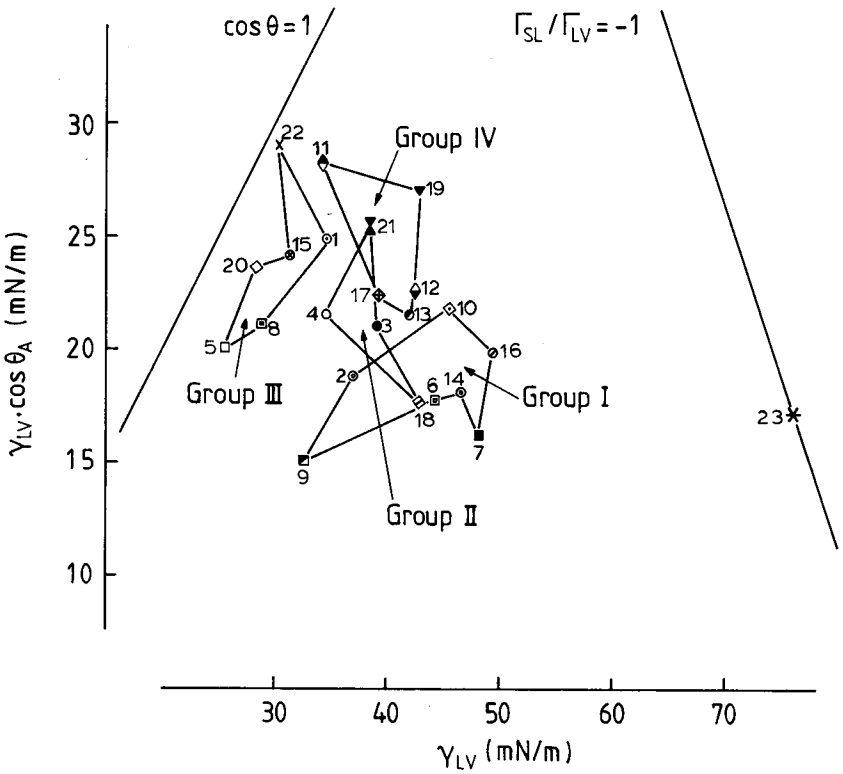

Fig. 6. Adhesion tension, $\gamma_{LV} \cos \theta$ vs surface tension, γ_{LV}, section for various surfactant solutions at a concentration of 10^{-1}% (w/v). (1) polysorbate 20 (2) polysorbate 60 (3) polysorbate 80 (4) polysorbate 85 (5) sorbitan monolaurate (6) sorbitan monopalmitate (7) sorbitan monostearate (8) sorbitan mono-oleate (9) sorbitan trioleate (10) poloxamine 304 (11) poloxamine 904 (12) poloxamine 908 (13) poloxamine 1508 (14) poloxamer 108 (15) poloxamer 184 (16) poloxamer 188 (17) poloxamer 338 (18) poloxamer 407 (19) polyoxyethylene (23) laurylether (20) sodium di (2-ethyl-hexyl)sulfosuccinate (21) Genapol PF 10 (22) Triton X-100 (23) water.

angles of phosphate-buffered saline and bovine serum (Table 4) after coating the plates with the surfactant solutions and subsequent drying. The higher bovine serum contact angles may be explained by the components of the serum: these serum components will not only interact with redissolving surfactant molecules in the serum, thus increasing the extent and rate of dissolution of the surfactants, but also compete with the surfactants for adsorptive sites on the solid–liquid interface. This adsorption of the serum components is reflected by the lowering of the advancing and receding contact angles on the clean surfactant-free surface.

As mentioned in the introduction, the surfactants investigated in this study were intended to be used for coating of colloidal drug carriers in order to alter the body distribution of these carriers after i.v. injection. Very few in-vivo studies with this latter objective were so far carried out and the surfactants were chosen heuristically (Leu et al., 1984; Illum and Davis, 1983, 1984; Davis and Illum, 1986; Illum et al., 1986, 1987). Nevertheless, the body distribution obtained with these empirically found substances differed quite considerably. Interestingly, all 4 surfactants used so far fall into different groups according to our classification (Table 5). Poloxamer 188 (Group I) leads to a significant liver uptake reduction and spillover into the spleen (Leu et al., 1984). This liver uptake reduction is especially pronounced shortly after injection and decreases with extended times (Leu et al., 1984; Illum et al., 1986). This is possibly a reflection of the comparatively low

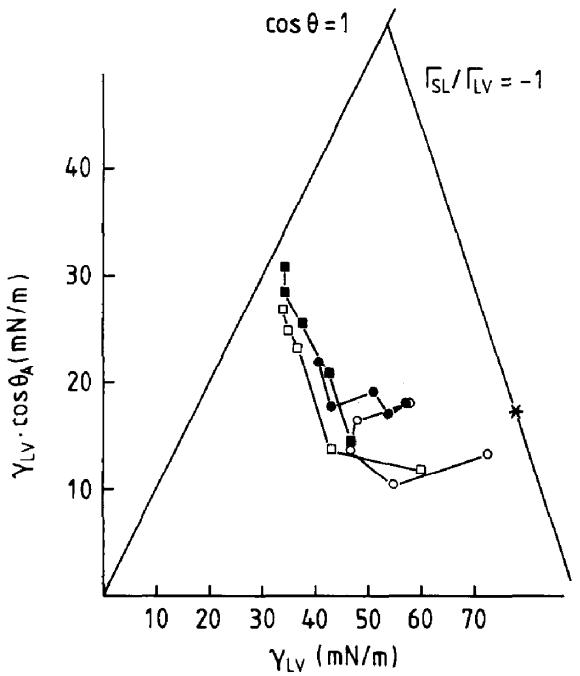

Fig. 7. Adhesion tension, $\gamma_{LV} \cos \theta$, vs surface tension, γ_{LV}, for aqueous solutions of representatives of the 4 surfactant groups listed in Tables 2 and 3: ○, sorbitan monostearate (Group I); ●, poloxamer 407 (Group II); □, polysorbate 20 (Group III); ■, poloxamine 904 (Group IV); *, water.

affinity of this surfactant to the polymer surfaces. Poloxamer 407 (Group II) is characterized by a very high liver uptake reduction and a very high bone marrow uptake. Poloxamer 338 and poloxamine 908 reduce the liver uptake to an intermediate level, increasing the distribution into the carcass profoundly. This liver uptake reduction and the resulting distribution into the carcass is considerably more pronounced with poloxamine 908 than with poloxamer 338. Although both surfactants fall into the same group according to our classification, poloxamine 908 shows zero contact angles at lower concentrations and a significantly larger hysteresis area, demonstrating a higher affinity to the polymer surface.

However, when comparing these results, it has to be kept in mind that the study of Leu et al. (1984) and the various studies of the group Illum and coworkers (Illum and Davis, 1983, 1984; Davis and Illum, 1986; Illum et al., 1986, 1987) differ in the polymer used, PMMA vs polystyrene. As demonstrated by Douglas et al. (1986), the polymer used also may have an influence on the body distribution of the surfactant-coated nanoparticles. Douglas et al. (1986), however, used a much more hydrophilic polymer, polybutylcyanoacrylate. With this polymer, the interaction and the affinity to the surfactants may be different. PMMA and polystyrene on the other hand are both more similar in their hydrophobicity (Kreuter et al., 1988), and a more similar affinity of the surfactants to the polymer surfaces may be expected.

The nanoparticles used in the above-mentioned studies also differ in the employed radioactive labelling method: Leu et al. utilized a ^{14}C-label located in the polymer chain thus assuring the stability of the label. They also determined the radioactivity of each organ at each time point individually. Illum et al. on the other hand used an iodine-label grafted onto the polymer by gamma irradiation (Illum and Davis, 1983). This label may not be as stable as a ^{14}C-label in the polymer chain. In addition, the use of a gamma camera outside the body does not allow such an accurate quantitative determination of the radioactivity as liquid scintillation counting of individual organs.

For this reason, the hypothesis brought forward in this paper, that surfactants may be classified into 4 different groups according to their interaction with the polymer surface and that this interaction in turn may influence the body distribution has to be challenged using different surfactants out of each group preferentially by using nanoparticles with a ^{14}C-label within the polymer chain.

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