Controlled Drug Release from Gels Using Surfactant Aggregates. II. Vesicles Formed from Mixtures of Amphiphilic Drugs and Oppositely Charged Surfactants

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Purpose. The aim of this study was to control the release of charged drugs from gels by adding surfactants that can interact with the drug and polymer matrix.

Methods. The *in vitro* release from gels was measured by using 6-mL gel holders immersed in 250 mL of simulated tear fluid and detecting the ultraviolet absorbance on-line. Gels were characterized by using a controlled rate rheometer, and surfactant aggregates were characterized by using cryo-transmission electron microscopy.

Results. The diffusion coefficient of alprenolol was $2.8 \cdot 10^{-6}$ cm^2/s in a lipophilically modified poly(acrylic acid) gel without surfactants present and $0.14 \cdot 10^{-6}$ cm^2/s when formulated with 1% sodium dodecyl sulfate. For fluvastatin, the diffusion coefficient changed from $3.0 \cdot 10^{-6}$ cm^2/s to $0.07 \cdot 10^{-6}$ cm^2/s in the presence of 0.2% benzyldimethyldodecyl-ammonium bromide. Alprenolol, betaxolol, metoprolol, diphenhydramine, and fluvastatin formed vesicles with oppositely charged surfactants in physiologic salt conditions.

Conclusions. In this article we show that it is feasible to control the release of charged drugs from gels by using surfactants. Vesicles are generally formed when surface active drugs are mixed with oppositely charged surfactants in physiologic conditions. The strongest effects on the release rate are seen for lipophilically modified polymer gels in which the drug and the oppositely charged surfactant form vesicles, but systems with micelles also give a slower release.

KEY WORDS: gel; Carbopol; controlled release; surfactants; vesicles; charged drugs.

INTRODUCTION

Gels are often used for cutaneous, ocular, and nasal drug delivery because they give a high drug absorption, often provided by the long residence time of the formulation at the site of absorption. A long residence time, caused by the rheologic properties of the gel, would only be advantageous if the drug remains in the formulation and is released throughout this time. Sustained release can be achieved if the drug is suspended in the gel as particles (1), distributed to liposomes (2), or if the drug interacts with the polymer (3). It has also been shown that surfactants can be used to give a prolonged release from gels through the partition of drugs to micelles (4). However, this procedure is limited to uncharged drug substances with a suitable log *D*. For charged drugs there is an even greater need to sustain the release and improve the absorption.

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In this article, surfactants are added to dissolved and charged drugs in gels. In such a system there can be three kinds of interactions affecting the drug release: (i) the drug substance can interact with the polymer, (ii) the drug can interact with the surfactants, and (iii) the surfactant can interact with the polymer matrix. The hypothesis of this study is that the release of a charged drug from a gel can be successfully controlled by using these interactions.

Five different types of gels were made: one physical gel, Gelrite®, and four covalently cross-linked poly(acrylic acid) hydrogels, Carbopol® 934, Carbopol® 981 and Carbopol® 940, which differ in the degree of cross-linking, and Carbopol® 1342, which has a covalently bound, lipophilic modification. Gelrite® is a cation-sensitive *in situ* gelling polysaccharide that seems to perform very well in humans (5). A series of three surfactants was used: the nonionic Brij 58, the anionic sodium dodecyl sulfate (SDS), and the cationic benzyldimethyldodecyl-ammonium bromide (BAB).

In this study, we chose a series of drugs that are all predominantly charged at physiologic pH and some are amphiphilic. In this way, we hope to reflect the range of charged substances that can be considered in gel formulations.

MATERIALS AND METHODS

Materials

Alprenolol hydrochloride, atenolol, diphenhydramine hydrochloride, metoprolol tartrate, Brij 58 (polyoxyethylene 20 cetyl ether), benzalkonium in the form of the pure homologue BAB, and SDS were purchased from Sigma (St. Louis, MO). Fluvastatin sodium was provided by AstraZeneca (Mölndal, Sweden). Betaxolol was a gift from Alcon (Stockholm, Sweden). See Table I and Fig. 1 for drug characteristics. Poly(acrylic acid) polymers with the proprietary names Carbopol 934P (C934), Carbopol 940NF (C940), Carbopol 981 (C981), and Carbopol 1342NF (C1342) were gifts from BF Goodrich (Brecksville, OH). Deacetylated gellan gum (Kelcogel F), also called Gelrite, was a gift from the Kelco division of the Monsanto Company (San Diego, CA). All other chemicals were from Sigma Chemical Co. and were of analytic or "ultra" quality. Ultrapure water, prepared by using a MilliQ Water Purification System (Millipore, France), was used in all preparations.

Preparation of Samples

The composition of simulated tear fluid was adopted from a tear fluid analysis (6) using 8.3 g NaCl, 0.084 g $CaCl_2 \cdot 2H_2O$, 1.4 g KCl in 1 L of ultrapure water. This is equal to 142 mM of Na^+, 19 mM K^+, and 0.6 mM of Ca^{2+}. All gels were prepared by weighing. The concentration of alprenolol, atenolol, betaxolol, diphenhydramine, and metoprolol was 18 mM in all gels except when otherwise stated. The concentration of fluvastatin was 3.6 mM. The concentration of surfactants was 1% for SDS and Brij 58, except when otherwise stated, and 0.2% for BAB.

Preparation of Carbopol Gels

The polymer powder was dispersed in simulated tear fluid containing the dissolved model drug with or without

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Table I. Characteristics of Drug Substances and Surfactants Used in the Release Experiments

Drug	MW	pK_a	Log *P*	Log *D*	Charge	CMC
Atenolol	266	9.6	0.16	–2.04	+	slightly surface active[a]
Metoprolol	267	9.7	1.88	–0.42	+	surface active, no CMC[b]
Alprenolol	249	9.7	2.65	0.40	+	100 mM[a]
Betaxolol	307	9.8	2.81	0.41	+	100 mM[a]
Fluvastatin	388	4.6	3.80	1.00	–	10 mM[c]
Diphenhydramine	255	9.0	3.30	1.69	+	120 mM[d]
Surfactant					Charge	CMC[e]
SDS	288				–	8 mM
BAB	384				+	8 mM
Brij 58	1120				0	7 μM

[a] Determined as described in Materials and methods.
[b] Ref. 17.
[c] Ref. 18.
[d] Ref. 19.
[e] According to the manufacturer, measured in water.

surfactants. The dispersions were then stirred by using magnetic stirring bars for approximately 1 h at room temperature, and eventually 1 M or 2 M NaOH, depending on the polymer concentration, was added to neutralize the sample to pH 6.5–7. For some formulations (footnote *d* in Table II), the solutions of drugs and surfactants were prepared and then mixed in the ratio 1: 1 with neutralized gel. All gels were allowed to equilibrate for at least 16 h at room temperature. The pH of the gels was then adjusted to pH 7.4, simulated tear fluid was added to achieve the final volume, and the gels were left for at least 90 min before measurement commenced. The polymer content of all Carbopol gels was 1%, except where otherwise stated.

Preparation of Gelrite Gels

The polymer powder was dispersed in ultrapure water, which contained dissolved surfactant for some systems. The dispersions were then stirred for 20 min at 100°C by using a water bath. The model substances were added during the cooling to room temperature, and then the solutions were allowed to equilibrate for at least 16 h. The polymer content of all Gelrite gels was 0.5%.

Drug Release Measurements

Drug release from the gels was measured by the USP paddle (XXI) method using gel containers with a fixed volume of 6 cm^3 and a surface area of 21 cm^2, covered by a coarse mesh-size plastic net and a stainless steel net. In this way, the gels were not allowed to swell. The containers were immersed in 250 mL of simulated tear fluid maintained at 35°C and stirred at 20 rpm by using a Pharma Test PTW II USP bath (Pharma Test, Apparatebau, Germany). The stirring rate was chosen so that it would give adequate convection and minimize surface erosion of the gels.

On-line measurements of the concentration were performed by continuously pumping the dissolution media by using a peristaltic pump and ismaprene tubing (Ismatec SA, Zürich, Switzerland) coupled to a ultraviolet (UV)-vis spectrophotometer, Shimadzu UV-1601 (Shimadzu, Kyoto, Japan). The absorbance was measured every 150 s for the first 45 min, then at 65 min and eventually every 30 min until the last measurement was made 6 h after the first one. The maximum absorbance wavelength was found to be 274 nm for atenolol, 271 nm for alprenolol, 275 nm for metoprolol and betaxolol, 258 nm for diphenhydramine, and 303 nm for fluvastatin.

The light scattering of polymer released from the gel at the very end (approximately after 4 h) of the experiment was compensated for by subtracting the absorbance from a drug-free experiment.

Diffusion Coefficient Calculation

One-dimensional fickian diffusion from a gel holder can under sink conditions during the initial part of the release, be expressed by:

$$Q = 2C_0\left(\frac{Dt}{\pi}\right)^{1/2} \quad (1)$$

where Q is the amount of drug released per unit area, C_0 is the initial concentration of the drug in the gel, D is the diffusion coefficient of the drug in the gel, and t is the time elapsed since the release experiment started. The equation is valid for the first 60% of the fractional release (7,8).

In our laboratory setting, the gel was placed in a confined space and was not allowed to swell during the study. Plots of the initial drug release vs. the square root of time should give a straight line, and the diffusion coefficient can be calculated from the slope of the line.

Rheologic Measurements

The rheologic measurements were carried out by using a Bohlin VOR Rheometer (Bohlin Reologi, Lund, Sweden), a controlled rate instrument of the couette type, in the dynamic oscillation mode. A concentric cylinder measuring system (C14) was used, and silicone oil was added onto the surface of the sample to prevent evaporation. All measurements were performed within the linear viscoelastic region at 35°C. Gelrite gels were studied by using temperature sweeps over the range 90–5°C, with a cooling rate of 0.5°C/min. as described elsewhere (9).

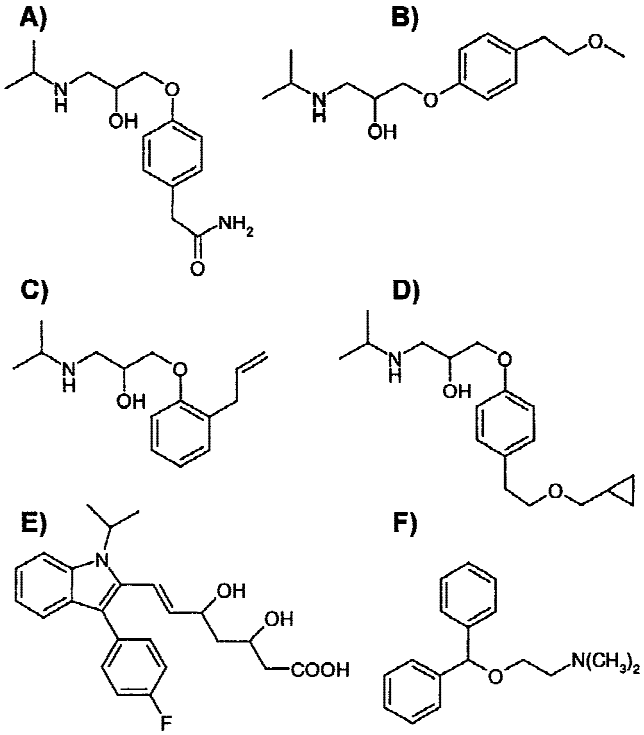

Fig. 1. Structure of the model substances studied: (a) atenolol, (b) metoprolol, (c) alprenolol, (d) betaxolol, (e) fluvastatin, (f) diphenhydramine.

Cryogenic Transmission Electron Microscopy

Cryogenic transmission electron microscopy (Cryo-TEM) was used to characterize drug-surfactant aggregates both in polymer-free solutions and in gels. A small drop of the sample was deposited on a grid covered by a polymer film, the excess liquid was blotted with filter paper, and the remaining sample on the grid was vitrified in liquid ethane. The films were transferred to a Zeiss EM 902 transmission electron microscope and kept below –165°C during the viewing procedures. All observations were made in the zero-loss bright-field mode at an accelerating voltage of 80 kV. Details of the method are described elsewhere (10).

Determination of Surface Tension

A duNoüy 8551 Tensiometer (Krüss, Hamburg, Germany) was used to measure the surface tension of drug solutions in simulated tear fluid after 10 min of equilibration time at room temperature. The critical micelle concentration (CMC) was obtained from plots of the surface tension vs. the logarithm of drug concentration.

Statistical Analysis

The 95% confidence interval was calculated for the slope of the line when fraction released was plotted as a function of $\sqrt{t}$. Data presented in the figures are means ± SD for $n = 3$ except when otherwise stated.

RESULTS AND DISCUSSION

Aqueous Mixtures of Drugs and Surfactants

A mixture of 18 mM diphenhydramine and 1% (36 mM) SDS in simulated tear fluid is quite turbid but homogeneous. Cryo-TEM images of the mixture reveal that the light scattering is caused by the presence of vesicles (Fig. 2a). When the positively charged, surface active drug diphenhydramine and the negatively charged surfactant SDS are mixed, vesicles are spontaneously formed. The mixture is prepared by using an ordinary magnetic stirrer resulting in vesicles having a very wide size distribution ranging from 50 nm to at least 900 nm. The vesicles are unilamellar or oligolamellar, and some have open membranes. The presence of flaws (Fig. 2b) in the vesicle surface is, however, not a major concern because the drug is not encapsulated in the vesicle but, instead, is a part of the vesicle bilayer.

The formation of vesicles can take place in a fairly wide range of drug:surfactant ratios, however, decreasing the amount of SDS to half (0.5%), a level that is equimolar to the diphenhydramine concentration, results in lost stability and a two-phase system. Vortex treatment and subsequent cryo-TEM confirms the presence of vesicles in addition to the droplets of the momentarily dispersed phase (Fig. 2c). Using double the SDS concentration (2%) produces a clear solution with high viscosity. Cryo-TEM shows long threadlike and highly branched micelles forming a bicontinuous structure (Fig. 2d). Bicontinuous threadlike micelles have previously been reported for equimolar mixtures of cetylpyridinium chloride and sodium salicylate (11). The ions present in the simulated tear fluid will affect the formation of the vesicles and the threadlike micelles. An increased ionic strength often causes micellar growth due to the shielding of the charges of the head groups. The shear viscosity of the sample shown in Fig. 2d (18 mM diphenhydramine, 2% SDS, prepared in simulated tear fluid) is 130 mPas (at 35°C, shear rate 100 s^{-1}). The same mixture prepared in 0.9% NaCl solution has a viscosity of 39 mPas and prepared in ultrapure water the viscosity is 1.1 mPas, which is close to the viscosity of water. These solutions are all totally clear.

In a concentration of 18 mM metoprolol, betaxolol, or alprenolol (Fig. 2b), vesicles are formed when mixed with 1% SDS. Also negatively charged drugs form vesicles when mixed with oppositely charged surfactants as was seen when fluvastatin was mixed with BAB. For charged drugs with less lipophilicity, e.g., atenolol, the amphiphilic properties are small, and mixtures of the drug with SDS produce clear solutions with unaffected viscosity, indicating no presence of vesicles or threadlike micelles.

Positively Charged Drugs and Negatively Charged Surfactants

Atenolol has a small but significantly slower release from C934 gels when 1% (35 mM) and 2% (70 mM) SDS is present (Fig. 3a). The aggregation number of SDS in physiologic salt solutions is approximately 80 (12), which will give approximately 0.5 mM SDS-micelles (1% SDS corresponds to 35 mM). However, in a PAA gel matrix, the aggregation number will be lower (13), resulting in a higher "concentration" of micelles, in addition to which, other types of aggregates than spherical micelles may form, which makes estimations of the aggregation number difficult. The drug concentration in the gels is 18 mM, which is in excess of the number of micelles. It is likely that atenolol interacts with the oppositely charged micellar surface, as has been discussed by Gerakis *et al.* (14), or that it forms mixed micelles.

Table II. Diffusion Coefficients (Mean ± 95% Confidence Interval) and Rheologic Characteristics of Gel Formulations at 1 Hz

Formulation	*Diff. coeff.* (10^{-6} cm^2/s)	G' (Pa)	G'' (Pa)
Pure C934[a]	—	65.4	5.98
Pure C1342[a]	—	123	7.32
Alprenolol,[b] C1342[a]	2.78 ± 0.10	182	42.1
Alprenolol,[b] C1342,[a] SDS (0.5%)	0.264 ± 0.018	235	22.4
Alprenolol,[b] C1342,[a] B58 (1%)	2.29 ± 0.13	157	47.2
Alprenolol,[b] C1342,[a] SDS (1%)	0.141 ± 0.002	258	24.0
Alprenolol,[b] C934[a]	6.31 ± 0.23	68.9	6.55
Alprenolol,[b] C934,[a] SDS (1%)	0.312 ± 0.023	51.0	4.95
Alprenolol,[b] Gelrite (0.5%)	6.32 ± 0.16	0.02–10[4c]	
Alprenolol,[b] Gelrite (0.5%), SDS (1%)	0.340 ± 0.032	0.02–10[4c]	
Atenolol,[b] C1342[a]	3.50 ± 0.22	131	11.3
Atenolol,[b] C1342,[a] SDS (1%)	1.59 ± 0.11	88.1	10.5
Atenolol,[b] C934[a]	6.02 ± 0.26	65.4	4.46
Atenolol,[b] C934,[a] SDS (2%)	3.05 ± 0.32	32.6	3.21
Atenolol,[b] C934,[a] SDS (1%)	3.89 ± 0.26	46.0	4.51
Atenolol,[b] C940[a]	4.49 ± 0.24	237	7.80
Atenolol,[b] C940,[a] SDS (1%)	2.02 ± 0.21	152	8.21
Atenolol,[b] C981,[a] SDS (1%)	2.00 ± 0.10	53.8	5.28
Atenolol,[b] Gelrite (0.5%), SDS (1%)	4.37 ± 0.26	0.02–10[4c]	
Diphenhydramine,[b] C1342[a]	4.00 ± 0.18	178[d]	43.2[d]
Diphenhydramine,[b] C1342,[a] SDS (1%)	0.136 ± 0.016	209[d]	64.5[d]
Diphenhydramine,[b] C934[a]	6.51 ± 0.27	55.8[d]	5.32[d]
Diphenhydramine,[b] C934,[a] SDS (1%)	0.239 ± 0.052	69.2[d]	7.41[d]
Diphenhydramine,[b] C934,[a] SDS (2%)	0.380 ± 0.093	39.3[d]	10.2[d]
Diphenhydramine,[b] C934,[a] SDS (0.1%)	4.36 ± 0.20	76.7[d]	4.49[d]
Fluvastatin,[b] C1342[a]	3.01 ± 0.11	154	12.6
Fluvastatin,[b] C1342,[a] BAB (0.2%)	0.0734 ± 0.0094	136	51.6
Fluvastatin,[b] C934[a]	5.91 ± 0.18	69.3	3.95
Fluvastatin,[b] C934,[a] BAB (0.2%)	0.200 ± 0.027	63.1	4.91
Metoprolol,[b] C1342[a]	3.68 ± 0.26	142	20.0
Metoprolol,[b] C1342,[a] SDS (1%)	1.30 ± 0.08	78.2	20.9
Metoprolol,[b] C934[a]	5.79 ± 0.21	68.7	4.20
Metoprolol,[b] C934,[a] SDS (1%)	2.21 ± 0.16	55.0	8.53
Betaxolol,[b] C934[a]	6.19 ± 0.26	77.1	3.25
Betaxolol,[b] C934,[a] SDS (1%)	0.321 ± 0.046	65.8	6.51
Betaxolol,[b] C1342[a]	3.42 ± 0.12	174	29.0
Betaxolol,[b] C1342,[a] SDS (1%)	0.198 ± 0.021	126	43.0

[a] Polymer concentration was 1%.
[b] The drug concentration was 18 mM for alprenolol, atenolol, diphenhydramine, metoprolol, and betaxolol except for fluvastatin, which was 3.6 mM.
[c] Gels formed *in situ* during the release experiment. The interval of the elastic modulus is shown.
[d] Gels prepared according to the alternative method, mixing neutralized solution with gel in the ratio 1:1.

The release of atenolol from four different gels in the presence of 1% SDS can be seen in Fig. 3b. C934 has the lowest cross-linking density according to the manufacturer and gives the fastest drug release. C1342 has a lipophilic modification that consists of a long-chain (C10-C30) alkyl acrylate, and it is probably the lipophilic interactions between the micelles and the polymer that results in the slower release from this gel. The concentration of lipophilic sites on the C1342 polymer is about 5–10 mM for a 1% gel (calculated by using the molecular weight of the monomer and the 5% differences in –COOH content between C1342 and C934 stated in the US National Formulary, XVIII ed.).

Although C981 and C940 differ in cross-linking density (C940 is more cross-linked), the release does not differ (Fig. 3b). It is likely that the mesh size of gels prepared from the two polymers gives the same obstructive effect on the SDS micelles.

When diphenhydramine and SDS are mixed in a gel (Fig. 2e), cryo-TEM shows that the size of the vesicles is similar to that in solution, but the vesicles have a faceted appearance due to interactions with the polymer, as has previously been reported for mixtures of SDS and didodecyldimethylammonium bromide (DDAB) in a hydroxyethyl cellulose (JR400) gel (15). By keeping the concentration of diphenhydramine constant but decreasing the SDS concentration the release from C934 gels can be seen in Fig. 4a. At 0.1% SDS the system is not homogenous, please compare with Fig. 2c, but some vesicles are present, and the release is significantly slower than without SDS. At 1% SDS, a greater proportion of the drug is present in vesicles and the release is also slower.

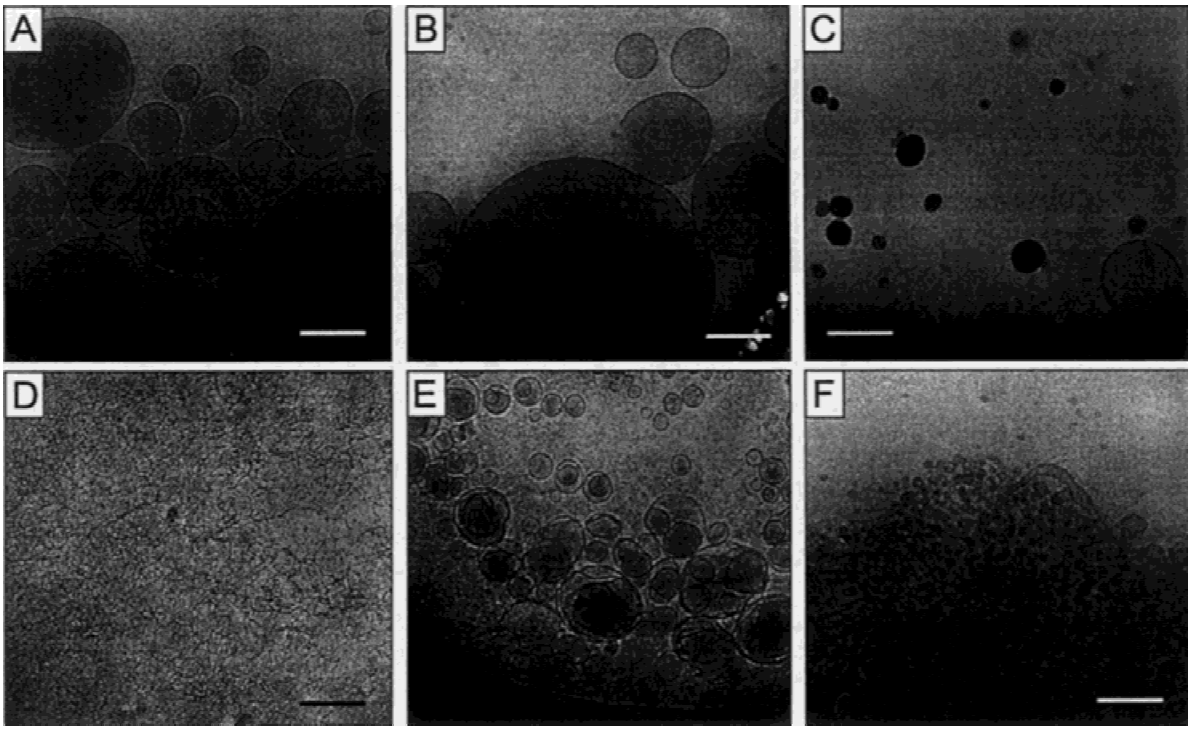

Fig. 2. Cryo-TEM images (bar = 200 nm) of (a) 18 mM diphenhydramine and 36 mM SDS (solution), (b) 18 mM alprenolol and 36 mM SDS in solution, (c) 36 mM diphenhydramine and 36 mM SDS (solution), (d) 18 mM diphenhydramine and 72 mM SDS (solution), (e) 18 mM diphenhydramine and 36 mM SDS in C934 gel, (f) 18 mM alprenolol and 36 mM SDS in C1342 gel.

At 2% SDS, however, the release is faster than the gel with 1% SDS because the drug is present in branched micelles, compare to Fig. 2d, instead of vesicles. These systems give less reproducible results (note the standard deviation in Fig. 4a).

In Fig. 4b it is shown that the release from C1342 gels with 18 mM alprenolol can be accurately controlled by varying the surfactant concentration. All formulations were homogeneous. The release can also be sustained by using surfactant mixtures where the charge density is decreased by mixing with nonionic surfactants. The formulation with 0.5% Brij 58 and 0.5% SDS in Fig. 4b gives a faster release than the 0.5% SDS formulation. With 1% Brij 58, alprenolol will probably form mixed micelles that will result in a somewhat slower release. Measuring the release of alprenolol from the C1342 gel with 1% SDS for 24 h shows a reproducible release rate and 25% has been released at the end point.

The addition of 1% C1342 polymer to the mixture of 18 mM alprenolol and 36 mM SDS shown in Fig. 2b gives the aggregates a completely different appearance (Fig. 2f) with very small vesicles, most of them not greater than 50 nm. It is interesting to note that the reproducibility of this system is very good, and measurements performed 2 months after the preparation show an identical release to those freshly prepared. Dilute solutions of hydrophobically modified polymer (the hydroxyethyl cellulose derivative LM200) were previously observed to induce formation of clusters of vesicles (15) or organized "bead-on-strings" structures of micelles using hydrophobically modified hydroxyethyl cellulose (HMHEC) (16).

Similar results, i.e., a sustained release of alprenolol and atenolol in the presence of SDS are also obtained when the *in situ* gel Gelrite is used (part of Table II). Several rheologic temperature sweep curves were prepared, but no changes in the gel forming ability could be detected (data not shown). This is a prerequisite when using *in situ* gels that are instilled as a drop and will form a gel when coming in contact with the tear fluid.

In Table II, rheologic characteristics and diffusion coefficients can be seen for metoprolol and betaxolol in addition to the above discussed positively charged substances. The release of metoprolol and betaxolol can be controlled by adding SDS and by the choice of polymer as discussed above. Vesicles are formed when the drugs are mixed with 1% SDS. When formulated in gels of C1342, the lipophilic modifications of the polymer can slow down the release by interacting with the lipophilic part of the drug and also interact with surfactant aggregates to give an even slower release.

Negatively Charged Drugs and Positively Charged Surfactants

The release of fluvastatin is slower from a C1342 gel than from a C934 gel (Fig. 5). This is caused by the differences in cross-linking density and, most likely, by the presence of lipophilic modifications in C1342. With the oppositely charged cationic surfactant benzalkonium bromide (BAB), the release can be sustained in the same way as for alprenolol in gels containing SDS. It is likely that vesicles are formed in this system too. Note that in these formulations the concentration of fluvastatin and BAB are both 1/5 of the concentration used for alprenolol and SDS. This is because the interaction between the cationic BAB and the anionic C1342 is so strong that with higher concentrations of BAB precipitation may occur.

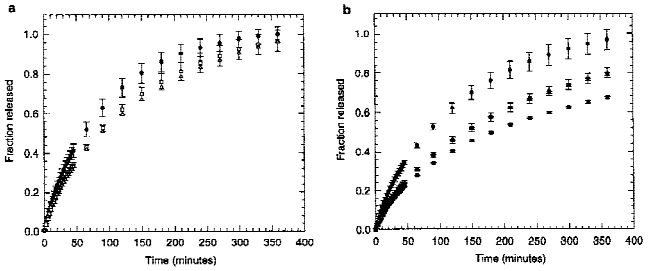

Fig. 3. (a) The release (mean ± SD, $n = 3$) of atenolol from C934 gels without surfactants (●), with 1% SDS (□) and with 2% SDS (△). (b) The release of atenolol from formulations with 1% SDS using 1% C934 (●), C981 (□), C940 (▲), and C1342 (■).

General Discussion

Figure 6 summarizes the diffusion coefficients of drugs with varying lipophilicities in different formulations. In the gels without surfactants, the diffusion coefficient varies only slightly. As reported previously, the interaction between an uncharged drug and Carbopol polymers does not give rise to a sustained release for drugs having log *D* values of 2 or less (4).

When oppositely charged surfactants are present, there is a dependence of the diffusion coefficient on the lipophilicity where the slowest release is observed for drugs with a log *D* greater than –1. Above this value, the drug forms vesicles with oppositely charged surfactant.

It is interesting that the small vesicles formed in C1342 give a slower release of drug than the bigger vesicles formed in C934. The lipophilic modifications of C1342 probably interact with the aggregates, resulting in a slower release.

The interaction between the polymer and drugs or surfactants can be seen from the rheological data presented in Table II. Amphiphilic drugs generally seem to increase the elasticity, G', of the gels, but the increase is also associated with an increased G''.

CONCLUSIONS

Vesicles are generally formed when drugs with amphiphilic properties and oppositely charged surfactants are mixed in certain ratios. This finding can be used to formulate gels with controlled release.

Furthermore, it has also been found that the higher the log *P* of a charged substance, the more interactions with surfactants and polymers can be anticipated, thus facilitating the formulation of a sustained release dosage form.

Finally, we conclude that the interactions between the surfactant aggregates and the polymer can be used to further influence the release. Further studies are needed to characterize the different phases seen when surfactants are mixed with oppositely charged drugs. Phase diagrams of the dilute region and the effects of ionic strength and different ions need to be considered and are currently being studied in our lab.

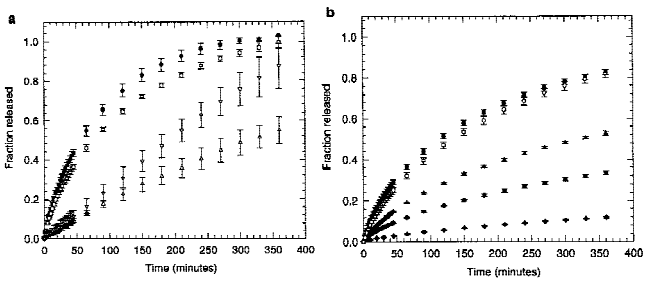

Fig. 4. (a) The release of diphenhydramine (mean ± SD, $n = 3$) from C934 formulations with no SDS (●), 0.1% SDS (□), 1% SDS (△), and 2% SDS (▽). (b) The release of alprenolol from C1342 gels with no SDS (■), 1% Brij 58 (○), 0.5% SDS + 0.5% Brij 58 (▲), 0.5% SDS (●), and 1% SDS (♦).

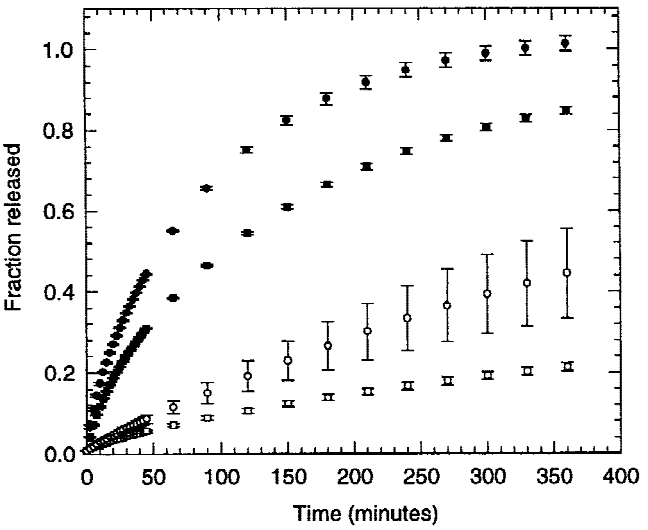

Fig. 5. The release (mean ± SD, $n = 3$) of fluvastatin from C934 (●), C1342 (■), C934 with 0.2% BAB (○), and C1342 with 0.2% BAB (□).

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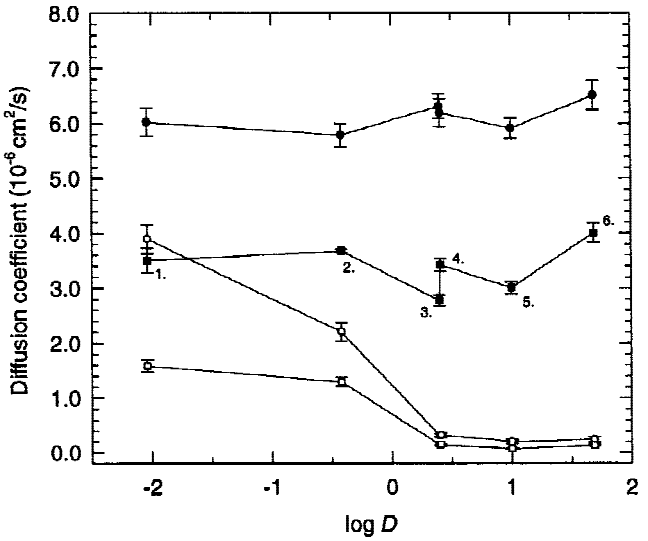

Fig. 6. The diffusion coefficient (mean with 95% confidence interval) of six drug compounds with varying lipophilicities (log *D* values) in C934 (●), C1342 (■), C934 with surfactants (○), and C1342 with surfactants (□). 1. atenolol, 2. metoprolol, 3. alprenolol, 4. betaxolol, 5. fluvastatin, 6. diphenhydramine.

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