Drug Development and Industrial Pharmacy, 25(7), 817–829 (1999)

Interfacial Adsorption of Polymers and Surfactants: Implications for the Properties of Disperse Systems of Pharmaceutical Interest

R. Duro, C. Souto, J. L. Gómez-Amoza,
R. Martínez-Pacheco, and A. Concheiro*

Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Santiago de Compostela, 15706 Santiago de Compostela, Spain

ABSTRACT

This review considers basic aspects of the interfacial adsorption of polymers and surfactants, with particular reference to the relevance of these processes for the formulation of pharmaceutical disperse systems. First, we discuss different approaches to the interpretation of adsorption isotherms, paying particular attention to systems containing more than one adsorbate. Second, we consider the implications of adsorption for the properties of suspensions, emulsions, and colloidal systems, particularly as regards the use of polymers and surfactants for stabilizing disperse systems, for controlling flocculation, and for modifying the biopharmaceutical behavior of colloidal drug carriers. Finally, we present a number of representative examples of the importance of adsorption of macromolecules in pharmaceutical systems.

INTRODUCTION

Polymers and surfactants are very commonly included in emulsion, suspension, and colloidal system dosage forms (1–3), generally with the aim of obtaining thickening or wetting effects. However, these components may have other effects, whether independently or as a consequence of interactions with other components (4,5), these effects being mostly due to electrostatic, steric, electrosteric, or depletion mechanisms. The tendency of polymers and surfactants to adsorb at interfaces is of great importance to these mechanisms (6) and to the in

---

* To whom correspondence should be addressed. Telephone: 3481594627. Fax: 3481547148. E-mail: ffancon@usc.es

www.dekker.com

vivo properties of colloidal pharmaceutical systems (7). As a result, the characterization of adsorption processes and adsorption films merits special attention. In what follows, we review basic aspects of interfacial adsorption in aqueous media, with particular regard to additives of this type and to implications for the properties of suspensions, colloidal dispersions, and emulsions of pharmaceutical interest. We stress the importance of taking these phenomena into account when optimizing dosage forms of these types.

INTERFACIAL ADSORPTION

General Considerations

Adsorption from solution can be seen as the result of competition between solvent and solute molecules for binding sites at an adsorbent surface. Such binding may be due to chemical or, more frequently, physical interactions. In general, adsorption involves London dispersion forces and forces due to specific interactions, mostly electrostatic (8).

Qualitative predictions about the adsorption of molecules in solution to solid surfaces are usually based on the following simple rules (9):

1. The quantity adsorbed is inversely proportional to the solubility of the adsorbate in the liquid phase (Lundelius rule).
2. In the absence of specific interactions between adsorbent and adsorbate, adsorption is poor.
3. The quantity adsorbed is proportional to the strength of the adsorbent-solute interaction and inversely proportional to the strength of the solvent-solute interaction.
4. In accordance with rules (2) and (3), and considering otherwise homologous systems, the amount adsorbed will vary in predictable fashion.

Adsorption of an adsorbate is typically a slower process than diffusion of that adsorbate in its solvent; this is due to cracks and pores in the adsorbing solid and to desorption and electrostatic repulsion. Furthermore, interfacial adsorption requires reordering of the molecules of adsorbate, which is of particular relevance when the adsorbate is a polymer. The affinity of the solvent for the adsorbate likewise influences the rate of adsorption, so that variables like pH, temperature, and the concentration of ions or other solutes may have an effect (6).

The characterization of adsorption processes, and the identification of the nature of the interactions involved, is usually based on the analysis of the corresponding adsorption isotherms. Figure 1 illustrates the classification of adsorption isotherms proposed by Giles et al. (10). Type L isotherms indicate the existence of nonspecific interactions between solute molecules and the adsorbent interface. Within this group, the most characteristic are L2-type isotherms, in which the flat region corresponds to the formation of a monolayer (i.e., adsorption reaches a saturation level). Nevertheless, adsorbate-adsorbate interactions may permit the formation of a multilayer film, giving L3-type isotherms.

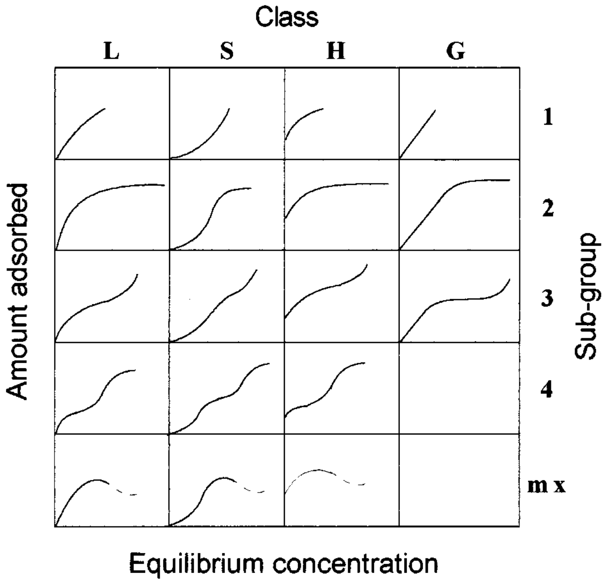

Figure 1. Giles et al.'s classification of adsorption isotherms (10).

Type L2 isotherms are typically described (11) by the Langmuir equation

$$\Gamma = \Gamma_\infty \cdot \frac{c}{c + (1/a)}$$

or by the Freundlich equation

$$\Gamma = k \cdot c^{1/n}$$

where Γ is the amount of solute adsorbed per unit surface at equilibrium concentration c of the solute in the solvent, Γ_∞ is the amount of solute necessary to form a complete monolayer, and a (adsorption activity), k, and n are constants.

The theoretical model underlying the Langmuir equation assumes that the solute is absorbed on a uniform surface, and that solute-solvent interactions (both at the adsorption interface and in the liquid phase) are negligible. By contrast, the Freundlich equation assumes that the adsorbent interface comprises a series of binding sites with exponentially distributed adsorption potentials (12): The values of the constants *k* and *n* depend on this distribution and provide information about (*a*) the amounts of solute necessary to saturate the adsorption monolayer and (*b*) the affinity of the solute by the adsorbent (13). It should be stressed that both equations are applicable only to dilute solutions and only describe monolayer adsorption.

Type S isotherms are sigmoid in shape. The most frequent are S2 isotherms, which indicate that adsorption occurs by two mechanisms until saturation (i.e., the flat region) is reached (14,15). These isotherms are not well described by the Langmuir or Freundlich equations. Tamamushi and Tamaki (16) proposed the use of a Brunnauer-Emmett-Teller (BET) type expression:

$$\Gamma = \frac{\Gamma_\infty}{(c_\infty - c)\{1 + (k - 1) \cdot c/c_\infty\}}$$

where c is the concentration of the solute at equilibrium, c_∞ is the concentration of the solute at saturation, and k is a constant.

By comparison with type L isotherms, type H isotherms (see Fig. 1) reflect higher affinity of the solute molecules for the adsorbent surface, generally as a result of chemical interactions (13).

Finally, a type G isotherm indicates that the solute distributes in constant proportion between the solution phase and the adsorbent surface.

Adsorption of Surfactants

The interpretation of surfactant adsorption is particularly complex since surfactant molecules may adopt various conformations in solution and may form various types of aggregate (15,17,18). In aqueous medium, the situation is made even more complex by the possibilities of ions being adsorbed to the interface (thus altering interface charge) and of ionization of the surfactant itself. The pH and ionic strength of aqueous media are thus of key importance, as has been demonstrated in numerous studies with various surfactants and adsorbents (19–24).

The nature of the adsorbent is likewise a key determinant of the adsorption process and of the characteristics of the adsorption film (25,26). If the adsorbent is apolar, adsorption is generally due to nonspecific interactions between surfactant hydrophobic groups and the adsorbent, giving rise to an adsorbate monolayer. In such cases, type L isotherms well fitted by the Langmuir equation are obtained (27–32). If the adsorbent is hydrophilic and the surfactant is ionic, adsorption is generally due to specific electrostatic interactions (33). If the adsorbent is hydrophilic and the surfactant is nonionic, a key role is typically played by donor-acceptor interactions between surfactant polar groups and the adsorbent surface, with hydrogen bonding being particularly frequent (34,35). In such cases, the formation of a monolayer film of surfactant molecules will make the adsorbent surface hydrophobic in character. If surfactant concentration increases sufficiently, an adsorption bilayer will form as a result of hydrophobic interactions between the nonpolar portions of adsorbed and nonadsorbed surfactant molecules, so that the surface recovers its hydrophilic character (36–38). Systems of this type give rise to type S isotherms (15,39). These considerations explain why adsorption processes involving surfactants are strongly dependent on their hydrophile-lipophile balance (40–42).

The role played in the adsorption of surfactants by ionic groups of the adsorbent has been detailed by Connor and Ottewill (43) in a study of the adsorption of hexadecyltrimethylammonium bromide by polystyrene particles (uncharged) and polystyrene latex particles (which bear carboxyl and hydroxyl groups at their surface). Adsorption to polystyrene was fitted by the Langmuir equation, whereas adsorption to polystyrene latex showed S-type isotherms as a result of electrostatic interactions and the consequent formation of an adsorption bilayer. Denoyel and Rouquerol (15) obtained similar results in a study of the adsorption of sodium octylbenzenesulfonate by alumina particles with different surface charges: A reduction in pH reduced the surface charge of the adsorbents and led to clear changes in the shape of the adsorption isotherms. Finally, Tiberg (44) observed the formation of bilayer films in a study of the adsorption by hydrophilic silica surfaces of various polyethyleneglycol monoalkyl ethers, all of which gave monolayer films when the adsorbent surface was hydrophobic.

The addition of electrolytes may have a marked influence on adsorption due to effects on the charge of the adsorbent surface (20,23). Furthermore, since the critical micelle concentration (CMC) of the surfactant generally declines as electrolyte concentration increases (15), and since the CMC typically coincides with the adsorption–film saturation concentration, the addition of electrolytes can be expected to lead to a reduction in saturation concentration (20).

Zhu and Gu (45) proposed the use of the following equation for interpreting adsorption isotherms (including type L and type S isotherms) when the adsorbate is a surfactant:

$$\Gamma = \Gamma_\infty \cdot \frac{k_1 c \cdot \left(\dfrac{1}{n} + k_2 c^{n-1}\right)}{1 + k_1 c \cdot (1 + k_2 c^{n-1})}$$

where k_1 and k_2 are the equilibrium constants for the first and second steps of the adsorption process, respectively, and n is the aggregation number of surface aggregates.

Adsorption of Polymers

Adsorption of polymers is typically due largely to hydrophobic interactions, though electrostatic interactions may be very important in cases in which the polymer and the adsorbent bear groups with opposite charge (3,6,26,46,47). In general terms, the adsorption of polymers accords with the rules previously outlined; however, the polymeric nature of these substances means that a number of other considerations must be taken into account (6).

First, the adsorption of a large linear polymer molecule is due to binding of particular sites; the remainder of the chain projects into the aqueous phase as tails or loops. The structure of the adsorption film varies as a function of the inherent variability in the conformation of the polymer molecules themselves and is dependent on the quantity of polymer adsorbed. At low coverage, the adsorbed layer is thin, and the polymer chains form ‘‘trains’’ at the surface; at high coverage, the more hydrophilic groups of the chain project into the aqueous phase to form tails and/or loops, and the adsorbed layer is thicker as a result of steric repulsion between these groups (48,49).

Second, the energies of the individual interactions between sites on the chain and the adsorbent surface are small, typically about 1 kT (5); since numerous sites on the chain are typically involved, however, the process tends to be irreversible (50).

Third, molecules of the same polymer but of different molecular weights may desorb at different rates. Thus, although lower molecular weight molecules tend to adsorb more rapidly, they tend to be replaced by higher molecular weight molecules, which desorb less rapidly (6).

Fourth, the characteristics of the medium and/or the polymer may occasionally be such as to encourage the formation of multilayer adsorption films. Such behavior has been reported in the adsorption of polyvinyl alcohol to various substrates (51,52) and of cellulose ethers to polystyrene latex and ibuprofen (53) and to pyrantel pamoate (32). In all cases, the formation of multimolecular films was inferred in view of deviations from the Langmuir model at high adsorbate concentrations.

Fifth, the adsorption of polymers is typically slow because of their high molecular weight and consequent slow rate of diffusion in the solvent. In view of this effect, Hsia, Shively, and Kildsig (54) have proposed an equation for predicting the rate of adsorption of polymers:

$$V = Kc \cdot (1 - \theta)$$

where K is the adsorption constant, c is the concentration of polymer in the medium, and θ is the proportion of adsorption sites occupied. In practice, interpretation of adsorption kinetics tends to be difficult since individual polymer molecules often adsorb to more than one site and since adsorbed molecules often interfere with access to unoccupied adsorption sites (48).

Recently, Kislenko et al. (55) developed a mathematical model of the kinetics of adsorption of polymeric substances to porous surfaces. Such surfaces are a source of additional complications. Equilibrium adsorption constants and adsorption and desorption rate constants derived from this model reflect the tendency of smaller molecules to be replaced by larger molecules at the adsorption surface. Furthermore, the model allows prediction of the maximum quantity of polymer that can be adsorbed per unit surface area.

The adsorption of macromolecules from dilute solutions can also be analyzed with the aid of the SFE model developed by Simha, Frisch, and Eirich (56):

$$\frac{\theta}{1 - \theta} \exp(2K_1\theta) = (Kc)^{1/v}$$

where θ is the proportion of the surface covered by adsorbed segments at concentration c, v is the mean number of segments adsorbed per polymer molecule, and K and K_1 are constants. This model allows the proportion of the surface covered to be related to an index of chain flexibility f, thus providing information on the configuration adopted by the adsorbed molecules by means of the expression

$$v = f^{(0.5nv^2)}$$

where n is the total number of segments in the chain.

The influence of chain structure on adsorption has been investigated in a number of experimental studies. Vaslin-Reiman, Lafuma, and Audebert (46) evaluated the relationship between the amount of an acrylamine/vinylimidazol copolymer adsorbed to silica particles and the proportion of vinylimidazol segments (i.e., the segments responsible for adsorption) in the chain. Van der Linden, Leermakers, and Fleer (57) found a clear relationship between the adsorption of different copolymers and the rigidity of their chains.

Duro et al. (32) compared the adsorption to pyrantel pamoate of two varieties of hydroxypropylmethylcellulose and two varieties of sodium carboxymethylcellulose and found considerable differences in amount adsorbed and in the structure of the adsorbed layer. The differences in adsorption are partially attributable to the high aqueous solubility, and thus low affinity for solid surfaces, of sodium carboxymethylcellulose. This polymer attaches to particle surfaces via one end of its chain, so that the thickness of the adsorption film is approximately the same as the length of a free molecule in solution. On the basis of the application of the SFE model to experimental data, this behavior has been attributed to the marked rigidity of carboxymethylcellulose molecules in medium of low ionic strength (56). In contrast, hydroxypropylmethylcellulose has more flexible chains and binds to solid surfaces at various points, giving rise to tails and loops that extend into the medium.

The following equation, derived from the model of Perkell and Ullman (58), is very useful for predicting (within a homologous series of polymers) the maximum amount of polymer adsorbed on the basis of its molecular weight M:

$$\log(\Gamma_{max}) = \log K + \alpha \cdot \log M$$

where K and α are constants related to the conformation adopted by the polymers at the adsorption interface. Experimental results obtained with cellulose ethers and polyvinylpyrrolidone meet the predictions of this model (32,53,56).

Finally, studies performed with various types of polymer have demonstrated the influence of pH on adsorption. This is attributable to the effects of this variable on the charge of both polymers and adsorption surfaces (59,60).

Adsorption in Complex Systems

In view of the above discussion, the interpretation of adsorption processes requires consideration of solute-adsorbent interactions, solute-solvent interactions, and solute-solute interactions. The effects of the introduction of a new component into the system will thus depend on effects on these interactions.

A number of studies have shown that the adsorption of a given surfactant may be affected by the presence of another surfactant (61). In some cases, the adsorption of the surfactant may be reduced by addition of a second surfactant of similar characteristics (62,63). In other cases, a surfactant that otherwise shows negligible adsorption may be induced to adsorb by the addition of a second surfactant (33,64). Of particular interest are the results obtained by Somasundaran and Huang (65) in a study of the adsorption to alumina of binary mixtures of ionic and nonionic surfactants. The adsorption behavior of surfactants in these mixtures was dependent on their concentration ratio; in some cases, the same two surfactants showed competitive or synergistic adsorption depending on their absolute and relative concentrations.

Polymer-surfactant interactions are particularly relevant since pharmaceutical disperse systems often contain components of both types. Many studies have demonstrated association between polymer chains and molecular aggregates of surfactants, often giving rise to marked changes in system properties (5,66,67).

A number of theoretical models have been proposed for the characterization of polymer-surfactant interactions in aqueous solution (see Ref. 5). Smith and Muller's (68) model considers each polymer molecule in the system to be comprised of a certain number of independent segments, each with mass Ms. Each segment may interact with n anions derived from the ionization of surfactant molecules. For the polyoxyethylene-(sodium dodecyl sulfate) system considered by these authors in the development of their model, they found n to be about 15; this is considerably lower than the about 100 molecules typically present in surfactant micelles, and the authors consequently denominated these aggregates *hemimicelles*.

Shirahama's (69) model permits estimation of the degree of association between a polymer and a surfactant using the following Langmuir-type expression:

$$\theta = \frac{Kc^n}{1 + c^n}$$

where n is the number of surfactant molecules forming part of the complex, c is the concentration of the surfactant, and K is a constant.

Finally, Nagarajan (70) has developed a more complex model that considers surfactant present as free molecules, as micelles, and as part of polymer-surfactant complexes. On the basis of kinetic analysis of the competitive processes of complexation and micelle formation, this model permits prediction of whether or not complexation will occur.

The degree of interaction is dependent on the nature and structure of the surfactant and the polymer (5,21, 67,71,72). In the case of polymers, the results of a number of studies have indicated that molecular weight is of key importance, and that—in the absence of ionization—interactions occur through their hydrophobic segments. Polymers typically interact most strongly with anionic surfactants, and the propensity with which an anionic surfactant interacts with polymers is related to the length of its alkyl chains (5,71). Cationic and nonionic surfactants tend to interact less strongly with polymers (73,74). Finally, if the two members of the pair are both ionic, aggregation may be impeded or facilitated by mutually repulsive or attractive electrostatic interactions (5,6,75).

The presence of polymers thus often has marked effects on the adsorption of surfactants, and vice versa, as a result of interactions in solution and of the typically reduced adsorption of polymer-surfactant aggregates. The most common outcome is that polymer adsorption is reduced (67,76–80). Sometimes, however, the surfactant may cause marked increases in the amount of polymer adsorbed as a result of the formation of polymer-surfactant aggregates at the adsorption surface (81).

Otsuka et al. (82) studied the adsorption of poly(vinylpyrrolidone) to silica particles of different hydrophilicities in the presence of various anionic surfactants. At low surfactant concentrations, they found that adsorption of the polymer was enhanced, particularly when the adsorbate was highly hydrophilic. At high surfactant concentrations, in contrast, adsorption was clearly impeded.

PHARMACEUTICAL IMPLICATIONS OF INTERFACIAL ADSORPTION

The effects of inclusion of polymers and surfactants (particularly polymeric surfactants) on the physical stability of disperse systems are very closely related to the adsorption processes these components undergo. Whether or not a given adsorption process will provoke stabilization or flocculation depends on the nature, structure, and concentration of the additive(s), together with the characteristics of the adsorbent and the liquid phase. In addition, the modification of the surface properties of colloidal particles by polymer or surfactant adsorption can change their biopharmaceutical behavior, which is a very interesting application of these phenomena. Detailed aspects related to these are discussed below.

Interfacial Adsorption and Steric Stabilization

Steric stabilization of a suspension is due to the formation of a film of adsorbed polymer molecules at the surface of the suspended particles; the nonadsorbed chains of these molecules extend into the liquid phase, hindering the approach of other particles and thus impeding aggregate formation (4).

For steric stabilization to be effective, adsorption thus must occur in such a way as to cover most of the adsorption surface with polymer, creating an adsorption film that is thick enough to counteract the forces of attraction between particles. Table 1 summarizes some studies of steric stabilization of suspensions, emulsions, and colloidal systems.

Suitable polymers thus must have sufficiently low water solubility to ensure effectively irreversible adsorption. At the same time, the nonadsorbed part of the chain must be sufficiently hydrophilic to extend into the liquid phase (99). As a result, amphipatic block copolymers (formed from homopolymers of different hydrosolubilities) are particularly effective (3,86,100,101). Other polymers (such as cellulose ethers, which have both hydrophilic and hydrophobic sections) interact with binding sites on the adsorption surface and at the same time show acceptable hydrosolubility (3,32,53,84,85,87,102). Finally, certain polymeric nonionic surfactants have also been reported to induce steric stabilization (31,83,88).

Flocculation can be induced in sterically stabilized systems by altering the affinity of the polymer for the liquid phase, which can be done by changing the temperature, pressure, or composition of the liquid phase (4). The level of the modified variable at which flocculation occurs is called the *critical flocculation point*. When two particles collide as a result of Brownian movement, a change occurs in the Gibbs free energy ΔG_F, the magnitude of this change being equivalent to the energy associated with the flocculation process, which is in turn the difference between the enthalpy component ΔH_F and the entropy component $T\Delta S_F$:

$$\Delta G_F = \Delta H_F - T\Delta S_F$$

If the system is to remain stable, ΔG_F therefore must be positive. This can be achieved by modifying the entropy component, the enthalpy component, or both components, giving rise to a three-way classification of steric stabilization processes (entropic, enthalpic, and combined entropic-enthalpic). The three types of process can be distinguished on the basis of the system's response to changes in temperature (4).

Steric stabilization due to the inclusion of more than one polymer in the system, known as *heterosteric stabilization*, is often particularly effective.

Stabilization is sometimes achieved by a combination of steric stabilization effects and electrostatic effects. The latter arise as a result of a net charge on the adsorbent surface that is not masked by the adsorption film and/or as the charge on the adsorbate molecules themselves (when these are ionic in nature). Stabilization of this type is referred to as *electrosteric stabilization* (4,103). The underlying mechanisms are complex as a result of effects of the charges on the conformation adopted by the macromolecules at the interface and in view of the effects of

Table 1

Studies of the Use of Interfacial Adsorption of Polymers and Surfactants for the Steric Stabilization of Suspensions, Emulsions, and Colloidal Systems

System Type	Adsorbent	Adsorbate	Ref. No.
Suspension	Aluminum hydroxide	Hydroxypropyl cellulose	85
		Polyvinyl alcohol–polyvinyl acetate copolymer	85
	Carbon black	Ethylene oxide surfactants	88
	Diloxanide furoate	Polyvinylalcohol	52
	Ibuprofen	Hydroxypropylcellulose	53, 84
		Hydroxypropylmethylcellulose	53, 84
	Mebendazol	Hydroxypropylmethylcellulose + polysorbate 80	87
		Sodium carboxymethyl cellulose + polysorbate 80	87
	Mica	Polymethyl methacrylate-polyethylene oxide copolymers	86
	Polystyrene latex	Hydroxypropylcellulose	53, 84
		Hydroxypropylmethylcellulose	53, 84
		Polymethyl methacrylate–polyethylene oxide copolymers	86
		Polyoxyethylenic surfactants	83
		Polyvinylalcohol	52
	Pyrantel pamoate	Hydroxypropylmethylcellulose	32
		Hydroxypropylmethylcellulose + polysorbate 80	67
		Polysorbate 80	31
		Sodium carboxymethylcellulose	32
		Sodium carboxymethylcellulose + polysorbate 80	67
Emulsion	Isoparaffinic oil	Polymethyl methacrylate–polyethylene oxide copolymer	90
		Polymethyl methacrylate–polyethylene oxide copolymer + sodium dodecyl sulfate	90
		Sodium dedecyl sulfate	90
	Linoleic acid	Cholesteryl-bearing pullulan	89
	Trioctanoylglycerol	Cholesteryl-bearing pullulan	89
Liposomes	Dipalmitoylphosphatidylcholine	Chondroitin sulfate	95
		Methacryloyloxyalkyl phosphorylcholine	94
	Monopalmitin	Polyvinylpyrrolidone	93
	Phosphatidylcholine	Chitosan	92
		Polyethylene oxide–polypropylene oxide copolymers	91
Nanoparticles	Poly(ε-caprolactone)	Poloxamer®	96
		Polyethyleneglycol 2000	96
		Polyvinyl alcohol	96
	Poly-2-iso-bucyanoacrylate, poly(lactic acid)	Poloxamer	96
		Polyethyleneglycol 2000	96
		Polyvinyl alcohol	96
	Poly(lactic acid-*co*-glycolic acid)	Poloxamer	96
		Polyethyleneglycol 2000	96
		Polyethyleneglycol-dextran conjugates	98
		Polyvinylalcohol	96
	Polyorganophosphazenes	Polyethylene oxide derivates of polyorganophosphazenes	97

Table 2

Studies of the Use of Interfacial Adsorption or Polymers and Surfactants for the Bridging Flocculation of Suspensions and Emulsions

System Type	Adsorbent	Adsorbate	Ref. No.
Suspension	Apatite	Polyacrylic acid	107
		Polyethylene oxide	108
	Cellulose (fibers)	Cationic polyacrylamide	109
		Poly(dialyldimethyl-ammonium chloride)	109
	Cellulose (microcrystalline)	Cationic polyacrylamide	109
		Poly(dialyldimethyl-ammonium chloride)	109
	Polystyrene	Bovine serum albumin	110
	Polystyrene latex	Polyacrylamide	111
		Polyelectrolytes	112
		Trimethylaminoethyl methacrylate	113
	Silica	Amylopectin	113
		Amylose	113
		Octylphenol polyoxyethylene	114
		Polyacrylamide	115
		Polyethylene oxide	116
Emulsion	Peanut oil	Sodium caseinate	117
	n-Tetradecane-bovine serum albumin	Carrageenan	118
		Dextran sulfate	119

the adsorption film on the characteristics of the double layer (104). The effects of polyelectrolytes on the stability of disperse systems must generally be explained in terms of both types of mechanism; in certain extreme situations, however, one may clearly predominate. Specifically, if ionic strength is low and the electrolyte is strongly ionized, electrostatic effects predominate, while when ionic strength is high and the electrolyte is weakly ionized, steric effects are more important (4,105).

Generally, steric stabilization is very useful for improving the physical stability of pharmaceutical suspensions and emulsions (31,32,53,106). Electrostatic stabilization is less commonly useful because its efficacy is relatively sensitive to electrolytes (4), which are commonly present in preparations of this type.

Interfacial Adsorption and Bridging Flocculation

One approach to the preparation of pharmaceutical disperse systems, as discussed in the previous section, is to prevent flocculation. Alternatively, it may be more practical to induce flocculation in such a way that the sediment can subsequently be resuspended by shaking (i.e., caking is avoided). One way of achieving such controlled flocculation is by the addition of polymers; once again, interfacial adsorption has important implications (Table 2).

Flocculation can be induced by the addition of low concentrations of certain polymers, generally of high molecular weight (4,116,120). When the particle concentration is high and the system is subjected to shaking, the polymer concentration range over which flocculation occurs is considerably extended (112,121). In such systems, flocculation is induced by the binding of different segments of the same polymer molecule to more than one particle, a phenomenon known as *bridging* (122). For a polymer to act in this way, it is necessary for the nonadsorbed chains or loops to extend into the medium for a distance greater than the minimum approach distance between particles (i.e., the distance beyond which electrostatic repulsion is negligible) (4).

The structure of the floccules formed in this way depends on numerous factors, including the energy of the polymer-particle interaction (123), the relationship between polymer concentration and particle concentration (124,125), the intensity of agitation (111,126), and the surface charge of the particles (110). However, the most important factor is the relationship between particle size and the molecular weight of the polymer; indeed, the length of the trailing polymer chains is largely dependent on this relationship (116). In this regard, three situations may arise (127):

Table 3

Studies of the Use of the Steric Effects of Interfacial Adsorption of Polymers and Surfactants to Change Biopharmaceutical Behavior of Colloidal Drug Carriers

System Type	Adsorbent	Adsorbate	Ref. No.
Microspheres	Polyethylene oxide–polystyrene copolymer	Methoxy polyethylene oxide	131
		Polyethylene oxide–polypropylene oxide copolymer	131
	Polystyrene	Methoxy polyethylene oxide	131
		Perfluoroalkylated phosphocholine	132
		Poloxamer	133, 134
		Poloxamine®	133, 134
		Polyethylene glycol phosphates	132
		Polyethylene oxide–polypropylene oxide copolymer	131
	Polystyrene latex	Poloxamer	135
		Poloxamine	135
Liposomes	Bovine hemoglobin-loaded liposomes	Carboxymethyl chitin	136
	Liposomally encapsulated bactericides	Positively charged stearylamine	137
	Phosphatidylinositol hemoglobin-loaded liposomes	Polyethylene glycol phosphatidylethanolamine	138
Nanoparticles	Polymethylmethacrylate	Antarox® DM 970	139
		Klucel® EF	139
		Poloxamer	140
		Poloxamine	139, 140
		Polysorbate	140
	Polystyrene	Poloxamer	141
	Polystyrene latex	Pluronic®	142
		Poloxamer	143
		Tetronic®	142
	Polyorganophosphazenes	Polyethylene oxide derivates of polyorganophosphazenes	97

1. The particles are much larger than the polymer molecules so that each polymer molecule adsorbs to only one particle.
2. The polymer chains are much larger than the particles so that several particles adsorb to each chain, forming multiparticle aggregates.
3. The particles and the polymer molecules are of similar size so that either of the above outcomes may result.

As a result, and in view of the characteristic size of polymer chains, flocculation is most readily achieved in systems with particles smaller than 50 μm in diameter. Flocculation of larger particles is hindered by the lower particle-polymer collision velocities, so that polymers do not adsorb. Furthermore, and since the interparticle bonds are weak, the floccules break up easily. In systems of this type, however, it is possible to induce bridging flocculation using high molecular weight polymers. Moudgil, Behl, and Prakash (107), for example, obtained flocculation of suspensions of apatite particles with diameter in excess of 100 μm using polyacrylic acid. If the polymer behaves like a surfactant, the micellar structures that form at the particle surface may play an important role in floccule formation (114).

Of the numerous polymers useful as flocculating agents, the most effective are typically high molecular weight polyelectrolytes, in view of the high charge density of their chains, which means that they tend to extend into the medium (4). If the polyelectrolyte molecules and the particle surface have opposite charges, flocculation may also be favored by charge neutralization; indeed, this may sometimes be the most important mechanism (113,128). The presence of ions in the medium has important effects on polyelectrolyte-induced flocculation. The compression of the double layer occurring as a result of the high ionic strength means that the molecular weight that the polymer must have in order to be an effective flocculating agent is reduced, even if its chains do not extend as far into the medium under such conditions (4).

Finally, as with steric stabilization, the efficacy of bridging flocculation may be improved by using more than one polymer (109,113,129).

Modification of the Surface and Biopharmaceutical Properties of Colloidal Drug Carriers

In recent years, the growing importance of liposomes and nanoparticle systems has created a further interest in so-called steric effects, not only for stabilization (91–97,130), but also as a means of controlling biopharmaceutical behavior (7) Table 3 lists some studies in this area. Specifically, interfacial adsorption of surfactants or polymers has been reported to be effective for (*a*) targeting and improving the efficacy of liposomes as carriers of drugs (144–146), (*b*) improving interaction between vaccines included in poly(DL-lactide-*co*-glycolide)-based microparticles and the corresponding binding sites in the target tissue (98), and (*c*) modifying interaction with blood components and organ distribution and reducing destruction by the mononuclear phagocyte system of liposomes and nanoparticles. In this field, the study of the phagocytosis of polystyrene latex particles, modified by the adsorption of poloxamer block copolymers, by human granulocytes (143) suggested that the hydrophilicity of the coating film is very important in determining the protective effect. So, this effect was found to increase with increasing length of the polyethylene oxide or polypropylene oxide chains. Other studies made with various nanoparticle systems coated with different surfactants and polymers are in accordance with this fact and conclude that it is possible to obtain information about the distribution of the drug carriers in the body by means of the study of the physicochemical properties, especially hydrophilicity, of the surface-modified particles (139–141).

ACKNOWLEDGMENTS

This work was supported by grant FAR 91-0293 from the CICYT, Spain.

REFERENCES

1. J. L. Zatz, J. Cosmet. Chem., 36, 393–411 (1985).
2. H. A. Lieberman, M. M. Rieger, and G. S. Banker, *Pharmaceutical Dosage Forms. Disperse Systems*, Vol. 2, 2nd ed., Marcel Dekker, New York, 1998.
3. G. J. Fleer, NATO ASI Ser., Ser. 3, 18, 269–283 (1996).
4. D. H. Napper, *Polymeric Stabilization of Colloidal Dispersions*, Academic, London, 1989.
5. E. D. Goddard, J. Soc. Cosmet. Chem., 41, 23–49 (1990).
6. R. Y. Lochhead, Cosmet. Toilet., 107, 131–156 (1992).
7. N. Emanuel, E. Kedar, O. Toker, E. Bolotin, and Y. Barenholz, in *Handbook of Nonmedical Applications of Liposomes*, Vol. 4 (D. Lasic and Y. Barenholz, Eds.), CRC Press, Boca Raton, FL, 1996, pp. 229–243.
8. F. M. Fowkes, ACS Symp. Ser., 15, 88–93 (1982).
9. S. Ross and I. D. Morrison, *Colloidal Systems and Interfaces*, Wiley-Interscience, New York, 1988.
10. C. H. Giles, T. H. MacEwan, S. N. Nakhwa, and D. Smith, J. Chem. Soc., 3973–3993 (1960).
11. D. J. Shaw, *Introduction to Colloid and Surface Chemistry*, 4th ed., Butterworth-Heinemann, London, 1980.
12. R. Sips, J. Chem. Phys., 18, 1024–1026 (1950).
13. D. K. Chattoraj and K. S. Birdi, *Adsorption and the Gibbs Surface Excess*, Plenum Press, New York, 1984.
14. D. Attwood, *Surfactant Systems*: *Their Chemistry*, *Pharmacy and Biology*, Chapman and Hall, London, 1983.
15. R. Denoyel and J. Rouquerol, J. Colloid Interface Sci., 143, 555–572 (1991).
16. B. Tamamushi and K. Tamaki, in *Proc. 2nd Int. Cong. Surface Activity*, Vol. 3, Butterworths, London, 1957, p. 449.
17. R. Sharma, ACS Symp. Ser., 615, 1–20 (1995).
18. D. M. Nevskaia, A. Guerrero-Ruíz, and J. D. López-González, J. Colloid Interface Sci., 181, 571–580 (1996).
19. S. Partyka, S. Zaini, M. Lindheimer, and B. Brun, Colloids Surf., 12, 225–270 (1984).
20. B. Brahimi, P. Labbe, and G. Reverdy, Langmuir, 8, 1908–1918 (1992).
21. Z. Ma, M. Chen, and J. E. Glass, Colloids Surf., A, 112, 163–184 (1996).
22. P. Chavez, W. Ducker, J. Israelachvili, and K. Maxwell, Langmuir, 12, 4111–4115 (1996).
23. T. P. Goloub, L. K. Koopal, B. H. Bijsterbosch, and M. P. Sidorova, Langmuir, 12, 3188–3194 (1996).
24. T. P. Goloub, L. K. Koopal, B. H. Bijsterbosch, and M. P. Sidorova, Langmuir, 13, 673–681 (1997).
25. S. Partyka, F. Thomas, J. Y. Bottero, E. Keh, and D. Cot, J. Calorim., Anal. Therm. Thermodyn. Chim., 17, 114–117 (1986).
26. Y. Zhang, M. Tirrell, and J. W. Mays, Macromolecules, 29, 7299–7301 (1996).
27. J. B. Kayes and D. A. Rawlins, Colloid Polym. Sci., 257, 622–629 (1979).
28. Th. van den Boomgaard, Th. F. Tadros, and J. Lyklema, J. Colloid Interface Sci., 116, 8–16 (1987).

29. K. Steinby, R. Silveston, and B. Kronberg, J. Colloid Interface Sci., 155, 70–78 (1993).
30. J. Zhao and W. Brown, J. Phys. Chem., 100, 5908–5912 (1996).
31. R. Duro, J. L. Gómez-Amoza, R. Martínez-Pacheco, C. Souto, and A. Concheiro, Int. J. Pharm., 165, 211–216 (1998).
32. R. Duro, C. Alvarez, J. L. Gómez-Amoza, R. Martínez-Pacheco, A. Concheiro, and C. Souto, Eur. J. Pharm. Biopharm., 45, 181–188 (1998).
33. L. Huang and P. Somasundaran, Colloids Surf., A, 117, 235–244 (1996).
34. B. Li and E. Ruckenstein, Langmuir, 12, 5052–5063 (1996).
35. A. Fan, P. Somasundaran, and N. J. Turro, Langmuir, 13, 506–510 (1997).
36. H. Rupprecht, Prog. Colloid Polym. Sci., 65, 29–44 (1978).
37. T. Nakamura and J. K. Thomas, Langmuir, 3, 234–239 (1987).
38. K. Meguro, T. Adachi, R. Fukunishi, and K. Esumi, Langmuir, 4, 1160–1162 (1988).
39. M.-R. Böhmer, L. K. Koopal, and R. Janssen, Langmuir, 8, 2228–2239 (1992).
40. K. G. Mathai and R. H. Ottewill, Trans. Faraday Soc., 62, 750–758 (1966).
41. P. H. Elworthy and W. G. Guthrie, J. Pharm. Pharmacol., 22, 114S–120S (1970).
42. P. Somasundaran, E. D. Snell, and Q. Xu, J. Colloid Interface Sci., 144, 165–173 (1991).
43. P. Connor and R. H. Ottewill, J. Colloid Interface Sci., 37, 642–651 (1971).
44. F. Tiberg, J. Chem. Soc., 92, 531–538 (1996).
45. B. Y. Zhu and T. Gu, J. Chem. Soc. Faraday Trans. 1, 85, 3813–3817 (1989).
46. S. Vaslin-Reimann, F. Lafuma, and R. Audebert, Colloid Polym. Sci., 268, 476–483 (1990).
47. A. K. Chakraborty and M. Tirrell, MRS Bull., 21, 28–32 (1996).
48. K. Chari, C. W. Frank, and A. Gast, Langmuir, 5, 1096–1105 (1989).
49. K. Eskilsson and F. Tiberg, Macromolecules, 30, 6323–6332 (1997).
50. K. Furusawa and T. Tagawa, Colloid Polym. Sci., 263, 353–360 (1985).
51. J. M. G. Lankveld and J. Lyklema, J. Colloid Interface Sci., 41, 475–483 (1972).
52. D. A. Rawlins and J. B. Kayes, Int. J. Pharm., 13, 145–158 (1983).
53. S. L. Law and J. B. Kayes, Int. J. Pharm., 15, 251–260 (1983).
54. D. C. Hsia, Ch. D. Shively, and D. O. Kildsig, Drug. Dev. Ind. Pharm., 4, 175–194 (1978).
55. V. N. Kislenko, A. A. Berlin, M. Kawaguchi, and T. Kato, Langmuir, 12, 768–773 (1996).
56. I. W. Kellaway and N. M. Najib, Int. J. Pharm., 6, 285–294 (1980).
57. C. van der Linden, F. A. M. Leermakers, and G. J. Fleer, Macromolecules, 29, 1172–1178 (1996).
58. R. Perkell and R. Ullman, J. Polymer Sci., 54, 127–148 (1961).
59. A. Yokoyama, K. R. Srinivasan, and H. S. Fogler, Langmuir, 6, 702–706 (1990).
60. M. Thomas, I. W. Kellaway, and B. E. Jones, Int. J. Pharm., 73, 185–190 (1991).
61. J. Brinck and F. Tiberg, Langmuir, 12, 5042–5047 (1996).
62. W. von Rybinsky and M. J. Schwuger, Langmuir, 2, 639–643 (1986).
63. K. Esumi, T. Nagahama, and K. Meguro, Colloid Polym. Sci., 269, 1274–1280 (1991).
64. P. Somasundaran, E. Fu, and Q. Xu, Langmuir, 8, 1065–1069 (1992).
65. P. Somasundaran and L. Huang, Polym. J. Chem., 71, 568–582 (1997).
66. I. Nahringbauer, Langmuir, 13, 2242–2249 (1997).
67. R. Duro, C. Alvarez-Lorenzo, C. Souto, J. L. Gómez-Amoza, R. Martínez-Pacheco, and A. Concheiro, Chem. Pharm. Bull., 46, 1421–1427 (1998).
68. M. L. Smith and N. Muller, J. Colloid Interface Sci., 52, 507–515 (1975).
69. K. Shirahama, Colloid Polym. Sci., 252, 978–981 (1974).
70. R. Nagarajan, Colloids Surf., 13, 1–17 (1985).
71. A. Carlsson, G. Karlström, and B. Lindman, J. Phys. Chem., 93, 3673–3677 (1989).
72. J. Ghodbane and R. Denoyel, Colloids Surf., A, 127, 97–104 (1997).
73. R. Nagarajan and B. Kalparci, in *Microdomains in Polymer Solution* (P. Dubin, Ed.), Plenum, New York, 1985.
74. E. Ruckenstein, G. Huber, and H. Hoffmann, Langmuir, 3, 382–387 (1987).
75. K. Hayakawa, J. P. Santerre, and J. C. T. Kwak, Macromolecules, 16, 1642–1645 (1983).
76. F. L. Saunders, in *Hydrophobic Surfaces* (F. M. Fowkes, Ed.), Academic, New York, 1969, pp. 131–138.
77. P. R. Sperry, H. B. Hopfenbreg, and N. L. Thomas, J. Colloid Interface Sci., 82, 62–76 (1981).
78. P. M. Claesson, M. Malmsten, and B. Lindman, Langmuir, 7, 1441–1446 (1991).
79. Ch. Ma and Ch. L. Li, Colloids Surf., 47, 117–123 (1990).
80. H. Otsuka and K. Esumi, J. Colloid Interface Sci., 170, 113–119 (1995).
81. Y. Yamanaka and K. Esumi, Colloids Surf., A, 122, 121–133 (1997).
82. H. Otsuka, K. Esumi, T. Ring, J. T. Li, and K. D. Caldwell, Colloids Surf., A, 116, 161–171 (1996).
83. D. A. Rawlins and J. B. Kayes, Int. J. Pharm., 13, 171–181 (1983).

84. S. L. Law and J. B. Kayes, Drug. Dev. Ind. Pharm., 10, 1049–1069 (1984).
85. M. M. Salazar-Gutiérrez, J. L. White, and S. L. Hem, Drug Dev. Ind. Pharm., 15, 17–24 (1989).
86. B. A. de L. Costello, P. F. Luckham, and T. F. Tadros, J. Colloid Interface Sci., 152, 237–246 (1992).
87. R. Duro, M. J. Vázquez, R. Martínez-Pacheco, J. L. Gómez-Amoza, A. Concheiro, and C. Souto, Pharmazie, 48, 602–605 (1993).
88. P. F. Luckham, A. I. Bailey, F. Miano, and T. H. Tadros, ACS Symp. Ser., 615, 166–188 (1995).
89. H. Fukui, K. Akiyoshi, and J. Sunamoto, Bull. Chem. Soc. Jpn., 69, 3659–3665 (1996).
90. R. Pons, P. Taylor, and T. F. Tadros, Colloid Polym. Sci., 275, 769–776 (1997).
91. K. Kostarelos, T. F. Tadros, and P. F. Luckham, Prog. Colloid Polym. Sci., 100, 206–211 (1996).
92. I. Henriksen, S. Vaagen, S. Sande, A. Sverre, G. Smistad, and J. Karlsen, Int. J. Pharm., 146, 193–203 (1997).
93. T. Sone, T. Hanamizu, M. Ichioka, T. Yokokura, S. Yoshikawa, I. Yoshio, K. Ikeda, and K. Esumi, Colloids Surf., A, 108, 273–279 (1996).
94. Y. Iwasaki, S. Tanaka, M. Hara, K. Ishihara, and A. Nakabayashi, Colloid Interface Sci., 192, 432–439 (1997).
95. A. Yoshida, H. Yamauchi, H. Sakai, N. Kawashima, and M. Abe, Colloids Surf., B, 8, 333–342 (1997).
96. C. Lourenço, M. Teixeira, S. Simoes, and R. Gaspar, Int. J. Pharm., 138, 1–12 (1996).
97. J. Vandorpe, E. Schacht, S. Stolnik, M. C. Garnet, M. C. Davies, L. Illum, and S. S. Davis, Biotechnol. Bioeng., 52, 89–95 (1996).
98. A. G. Coombes, S. Tasker, M. Lindblad, J. Holmgren, K. Koste, V. Toncheva, E. Schacht, M. C. Davis, L. Illum, and S. S. Davis, Biomaterials, 18, 1153–1161 (1997).
99. V. S. Stenkamp and J. C. Berg, Langmuir, 13, 3827–3832 (1997).
100. K. E. Barret, *Dispersion Polymerization in Organic Media*, Wiley-Interscience, London, 1975.
101. Ch. M. Wijmans, F. A. M. Leermakers, and G. J. Fleer, J. Colloid Interface Sci., 167, 124–134 (1994).
102. D. A. Rawlins and J. B. Kayes, Drug Dev. Ind. Pharm., 6, 427–440 (1980).
103. J. L. Ortega-Vinuesa, A. Martin-Rodriguez, and R. Hidalgo-Alvarez, J. Colloid Sci., 184, 259–267 (1996).
104. M. B. Einarson and J. C. Berg, J. Colloid Interface Sci., 155, 165–172 (1993).
105. K. R. Rogan, A. C. Bentham, I. A. George, and D. R. Skuse, Colloid Polym. Sci., 272, 1175–1189 (1994).
106. R. Y. Lochhead and C. J. Rulison, Polym. Mater. Sci. Eng., 69, 255–256 (1993).
107. B. M. Moudgil, S. Behl, and T. S. Prakash, J. Colloid Polym. Sci., 158, 511–512 (1993).
108. S. Behl and M. Moudgil, J. Colloid Interface Sci., 161, 422–429 (1993).
109. A. Swerin, G. Glad-Nordmark, and L. Odberg, J. Pulp Pap. Sci., 23, J389–J393 (1997).
110. A. Schmitt, A. Fernández-Barbero, M. Cabrerizo-Vilchez, and R. Hidalgo-Alvarez, Prog. Colloid Polym. Sci., 104, 144–147 (1997).
111. S. J. Peng and R. A. Williams, J. Colloid Interface Sci., 166, 321–332 (1994).
112. Y. Adachi and T. Matsumoto, Colloids Surf., A, 113, 229–236 (1996).
113. S. Wall, P. Samuelsson, G. Degerman, P. Skoglund, and A. Samuelsson, J. Colloid Interface Sci., 151, 178–188 (1992).
114. F. Giordano-Palmino, R. Denoyel, and J. Rouquerol, J. Colloid Interface Sci., 165, 82–90 (1994).
115. Y. Otsubo and K. Watanabe, J. Colloid Interface Sci., 122, 346–353 (1988).
116. S. F. Liu, V. Legrand, M. Gourmand, F. Lafuma, and R. Audebert, Colloids Surf., A, 111, 139–145 (1996).
117. E. Dickinson, M. Golding, and M. J. W. Povey, J. Colloid Interface Sci., 185, 515–529 (1997).
118. E. Dickinson and K. Pawlowsky, J. Agric. Food Chem., 45, 3799–3806 (1997).
119. E. Dickinson and K. Pawlowsky, J. Agric. Food Chem., 44, 2992–3000 (1996).
120. Y. Otsubo, Heterog. Chem. Rev., 3, 327–349 (1996).
121. V. Chaplain, M. L. Janex, F. Lafuma, C. Graillat, and R. Audebert, Colloid Polym. Sci., 273, 984–993 (1995).
122. J. Gregory, Spec. Publ.—R. Soc. Chem., 186, 62–75 (1996).
123. K. Wong, P. Lixon, F. Lafuma, P. Lindner, O. Aguerre-Charriol, and B. Cabane, J. Colloid Interface Sci., 153, 55–72 (1992).
124. Y. Otsubo, J. Colloid Interface Sci., 153, 584–586 (1992).
125. O. Spalla and B. Cabane, Colloid Polym. Sci., 271, 357–371 (1993).
126. K. Furusawa, Z. Shou, and N. Nagahashi, Colloid Polym. Sci., 270, 212–218 (1992).
127. J. P. Hsu and D. P. Lin, Colloid Polym. Sci., 274, 172–177 (1996).
128. Y. Adachi, M. A. Cohen-Stuar, and R. Fokking, J. Colloid Interface Sci., 171, 520–521 (1995).
129. F. Csempesz, Colloid J., 59, 80–86 (1997).
130. B. Seijo, C. Gutiérrez de Rubalcava, R. Duro, J. L. Rodríguez, and A. Concheiro, Proc. 2nd World Meeting APGI/APV, 663–664 (1998).
131. G. R. Harper, M. C. Davies, S. S. Davis, T. F. Tadros, D. C. Taylor, M. P. Irving, and J. A. Waters, Biomaterials, 12, 695–700 (1991).
132. N. Privitera, R. Naon, P. Vierling, and J. G. Ries, Int. J. Pharm., 120, 73–82 (1995).
133. M. E. Norman, P. Williams, and L. Illum, Biomaterials, 14, 193–202 (1993).
134. M. E. Norman, P. Williams, and L. Illum, J. Biomed. Mater. Res., 27, 861–866 (1993).

135. S. Stolnik, N. C. Felumb, C. R. Heald, M. C. Garnett, L. Illum, and S. S. Davis, Colloids Surf., A, 122, 151–159 (1997).
136. M. Mobed and T. M. S. Chang, Biomater. Artif. Cells Immobil. Biotechnol., 19, 731–744 (1991).
137. N. M. Sanderson and M. N. Jones, Pestic. Sci., 46, 255–261 (1996).
138. R. L. Sherwood, D. L. McCormick, S. Zheng, and R. L. Beissinger, Artif. Cells Blood Substit. Immobil. Biotechnol., 23, 665–679 (1995).
139. S. D. Troester, K. H. Wallis, R. H. Mueller, and J. Kreuter, J. Controlled Release, 20, 247–260 (1992).
140. R. H. Mueller, K. H. Wallis, S. D. Troester, and J. Kreuter, J. Controlled Release, 20, 237–246 (1992).
141. T. Blunk, M. Lueck, B. W. Mueller, and R. H. Mueller, World Meet. Pharm. Biopharm. Pharm. Technol., 1, 531–532 (1995).
142. J. S. Tan, D. E. Butterfield, C. L. Voycheck, K. D. Caldwell, and J. T. Li, Biomaterials, 14, 823–833 (1993).
143. S. Rudt and R. H. Mueller, J. Controlled Release, 25, 51–59 (1993).
144. Y. Barenholz, E. Bolotin, R. Cohen, and A. Gozon, Phosphorus, Sulfur Silicon Relat. Elem., 109–110, 1–4 Proc. 13th Int. Conf. Phosphorus Chemistry, 293–296 (1995).
145. M. Jones, Curr. Opin. Colloid Interface Sci., 1, 91–100 (1996).
146. D. Lasic, ACS Symp. Ser., 680, 31–44 (1997).