DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 66

Colloidal Drug Delivery Systems

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edited by
Jörg Kreuter

Colloidal Drug Delivery Systems

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ADDITIONAL VOLUMES IN PREPARATION

Preface

The efficacy of many drugs is often limited by their potential to reach their therapeutical site of action. In most cases, only a small amount of the administered dose of the drug reaches this site, while the major drug amount is distributed to the rest of the body depending on the physicochemical and biochemical properties of the drug. In contrast, a site-specific delivery would not only increase the amount of drug reaching the site but also simultaneously decrease the amount being distributed to other parts of the body, thus reducing unwanted side effects. Site-specific or targeted delivery, therefore, would also enable a reduction in the necessary dose to be administered. By decreasing the side effects, it would also increase the therapeutic index of the drug.

A more specific accumulation at the target site may be achieved by altering the chemical structure toward more suitable physicochemical and/or biochemical properties of the drug. This strategy involves the synthesis of either a totally new compound or a so-called prodrug from which the active drug is produced by the body's own metabolism. Although these approaches may be very successful in some cases, in others the synthesis of a more site-specific drug is not possible. For this reason, delivery of the original drug

by specially designed drug delivery systems is the better solution—and sometimes the only feasible one.

A large number of drug delivery systems have been conceived and developed. Among these systems, colloidal drug delivery systems hold great promise for reaching the goal of drug targeting.

The idea of drug targeting by such systems was originally formulated by Paul Ehrlich. After visiting the opera *Der Freischütz* by Carl Maria von Weber, in which so-called *Freikugeln* play a major role, Ehrlich came upon the idea of *Zauberkugeln*—magic bullets (1). The *Freikugeln* in the opera could be fired in any direction yet still reach their goal. Ehrlich imagined that similarly targeted tiny drug-loaded magic bullets would significantly improve therapy.

Because of their small particle size—below 1 μm—colloidal drug carriers come close to Ehrlich's idea. These drug delivery systems offer various advantages for many medical, agricultural, veterinary, and industrial applications.

Over the years, controlled drug delivery as well as site-specific delivery have made considerable advances. One area that contributed significantly to this progress is the rapidly developing field of submicron delivery systems—colloidal drug carriers. Although numerous reviews and books have been published concerning this topic, the rapid developments in the area of colloidal drug carriers make frequent updates a necessity.

This volume focuses mainly on the most widely investigated colloidal drug delivery systems: nanoparticles, liposomes and the related niosomes, and microemulsions. In addition, the book also sheds light on a somewhat forgotten fact, namely that some ointments also represent colloidal drug delivery systems.

The length of individual chapters may appear imbalanced—the chapters on nanoparticles and especially liposomes are much longer than the others. However, this organization was intended because much more work is presently being done and published in the liposome and nanoparticle fields than in the other areas.

The chapters in this book are arranged by increasing physical ordering and complexity, beginning with ointments, then describing the related but more particulate microemulsions, followed by the more solid liposomes and niosomes, and finally by solid system nanoparticles.

The editor thanks all contributors for their valuable work and Marcel Dekker, Inc., for its professional cooperation.

Jörg Kreuter

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1

Ointments and Creams as Colloidal Drug Delivery Systems

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I. INTRODUCTION

Ointments and creams have been used for many centuries to improve the healing conditions of wounds and to treat in empirical ways skin diseases as well as to retard the aging process of the skin and to preserve natural beauty. Dermatological preparations and cosmetics that represent the modern generations of these systems are also called semisolids due to their unique properties of being in the solid state under ambient conditions and being transformed to the liquid state when mechanically stressed during the application on the skin. These properties allow the systems to spread easily on the surface of the skin. Depending on the formulation, ointments in general remain on the surface of the skin and show skin protection and occlusion, whereas creams may be able to penetrate into the different layers of the skin, especially the stratum corneum (horny layer) and to exert interactions with both the keratines in the horny cells (corneocytes) and the lipid bilayers in which the horny cells are embedded.

Ointments are defined as water-free systems ranging from systems with extreme lipophilic properties (e.g., liquid paraffins, white petrolatum, and

paraffin waxes) to systems with good hydrophilic properties (e.g., polyethyleneglycol ointments). Ointments with medium polar character are W/O or O/W absorption bases (mostly lipophilic vehicles) in which O/W or W/O emulsifiers are incorporated. Addition of water to these absorption bases results in the formation of O/W or W/O creams, which are generally defined as water-containing systems. We speak of O/W creams when water forms the outer (continuous) phase and of W/O creams when the lipid phase is the outer phase. Creams may be viewed as simple O/W or W/O emulsions that are predominantly stabilized by a colloidal gel structure. In his pioneering work Münzel (1) described semisolids as plastic gels for cutaneous application.

The dominant colloidal structural elements of semisolid preparations are three-dimensional colloidal solid networks in which a liquid is incorporated. Such a bicoherent (spongelike) structure may be referred to as a gel. For this reason a differentiation in gels between continuous and dispersed phases is impossible because of the complete interpretation of the bicontinuous phases, whereas it is possible for emulsions and suspensions.

It is in fact this bicoherent gel structure of colloidal-sized structures, caused by van der Waals interactions and hydrogen bondings, that makes these systems different from the other colloidal drug carrier systems such as nanoparticles, liposomes, niosomes, etc. They preferentially exist in a dispersed state.

The gel structures of semisolid preparations may be either in a crystalline or in a liquid-crystalline state. The type of the gel structure mainly determines the systems' (1) rheological properties, (2) stability, (3) possible interactions with the skin, and (4) drug release. The knowledge of the colloidal structures of these semisolid systems is of essential importance for the understanding of the behavior of these systems and for their proper application on the skin.

In this chapter the colloidal structures of the most-used dermatological preparations, i.e., creams with crystalline and liquid-crystalline gel structures, will be presented, as well as some aspects of in vitro drug release and its dependence on the colloidal gel structures of these systems.

II. COLLOIDAL GEL STRUCTURES OF CREAMS

A. Colloidal Structures of O/W Creams

1. Water Containing Hydrophilic Ointment*

The formulation of Water Containing Hydrophilic Ointment DAB 9 (German Pharmacopoeia, 9th edition) is as follows:

*The German Pharmacopoeia, 9th edition, is not consistent in its definitions, and water containing hydrophilic ointment DAB 9 is a cream.

Emulsifying wax	9.0	% wt/wt
Liquid paraffins	10.5	% wt/wt
White petrolatum	10.5	% wt/wt
Water	70.0	% wt/wt

X-ray investigations by the Kratky low angle technique (SAXD) and by wide angle x-ray diffraction (WAXD) in combination with quantitative differential scanning calorimetry (DSC) led to the following structure model of Water Containing Hydrophilic Ointment DAB 9 (2–4). It was found that such O/W creams may be regarded as four-phase systems (Fig. 1). The dominant matrices are the hydrophilic and the lipophilic gel phases. Both gel phases form colloidal-sized mixed crystals consisting of surfactant bilayers. The surfactants in the bilayers are oriented in such a way that the hydrocarbon tails are directed toward each other, as are the polar groups (Fig. 1, region a). The hydrophilic gel phase consists of cetostearyl alcohol as well as the whole amount of the ionic sodium-*n*-alkylsulfates, which are randomly distributed within the cetostearyl alcohol molecules. The latter act as lateral spacers for the strong polar sodium-*n*-alkylsulfate molecules. In the crystalline bilayer structure therefore strong hydrophilic moieties and hydrophobic cores alternate with each other (Fig. 1, region a).

A part of the total water amount of the system is interlamellarly inserted between the polar groups of the surfactant molecules (Fig. 1, region b). This

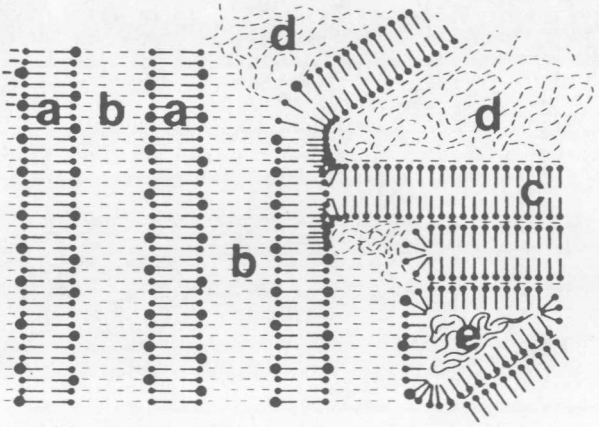

Figure 1 Gel structures of Water Containing Hydrophilic Ointment DAB 9. a, mixed crystal bilayer of cetostearylalcohol and cetostearylalcoholsulfates; b, interlamellarly fixed water layer; a + b, hydrophilic gel phase; c, lipophilic gel phase (cetostearylalcohol semihydrate); d, bulk water phase; e, lipophilic components (dispersed phase).

part of the water is called interlamellarly fixed water. The regions a and b together form the hydrophilic gel phase. The water molecules fixed interlamellarly in the hydrophilic gel phases are in equilibrium with the molecules of the bulk water phase (Fig. 1, region d). The bulk water phase is the liquid component of the gel structure, and the solid phase is the hydrophilic gel phase (although it contains part of the water interlamellarly bound). The bulk water is fixed within the network of the hydrophilic gel phase mainly by capillary attraction forces. Furthermore, it is assumed that the interlamellarly fixed water molecules exhibit other physicochemical properties than those of the bulk water phase.

The surplus of cetostearyl alcohol not incorporated in the hydrophilic gel phase builds up a separate matrix with lipophilic properties (Fig. 1, region c) called the lipophilic gel phase. The inner or dispersed phase (Fig. 1, region e) is mainly immobilized mechanically by this lipophilic gel phase. The lipophilic gel phase consisting of pure cetostearyl alcohol is only able to form a semihydrate with water.

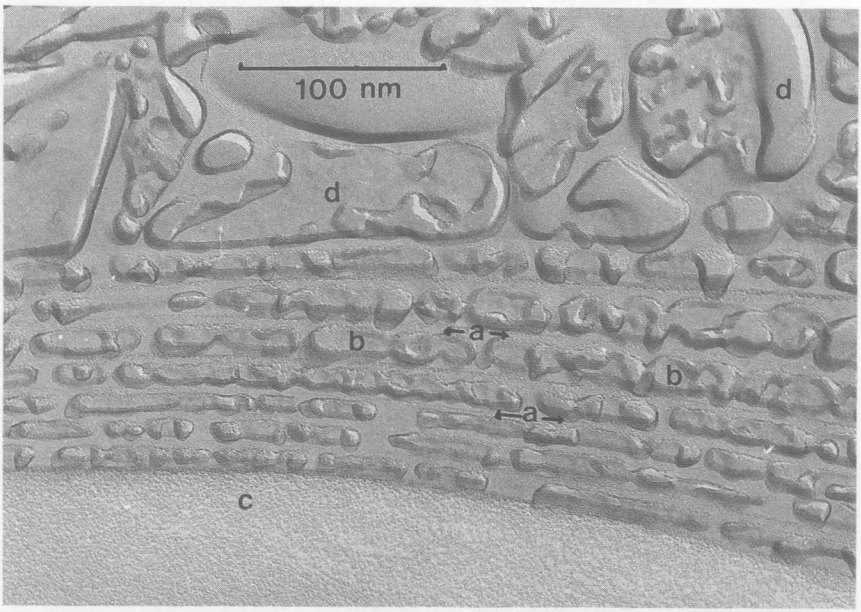

Figure 2 Freeze fracture micrograph of Emulsifying Wax DAB 9 (main structural component of Water Containing Hydrophilic Ointment DAB 9) with 70% (wt/wt) water. a, mixed crystal bilayer; b, interlamellarly fixed water; a + b, hydrophilic gel phase; c, fracture edge of a lipophilic plane; d, bulk water phase.

Freeze fracture electron microscopy (FFEM) has added a new dimension to the studies of colloidal O/W cream organization. This technique allows the visualization of the previously mentioned structural elements (5–7). From Fig. 2 the hydrophilic gel phase can be recognized very clearly. In this photograph the alternating layers of the hydrophilic gel phase are nearly rectangular to the fracture plane. Together with areas of bulk water d entrapped in the hydrophilic gel phase, the interlamellarly bound layers of water b and the bilayers of the surfactant molecules a are visible. Together, a and b form the hydrophilic gel phase.

Investigations about the swelling ability of Emulsifying Wax DAB 9 (main surfactant component of Water Containing Hydrophilic Ointment DAB 9) with water (Fig. 3) show a swelling of the lamellar gel structure when the long spacings as obtained from small angle x-ray diffraction (SAXD) are plotted versus the ratio water/surfactant (wt/wt) (see Fig. 3, where C is the

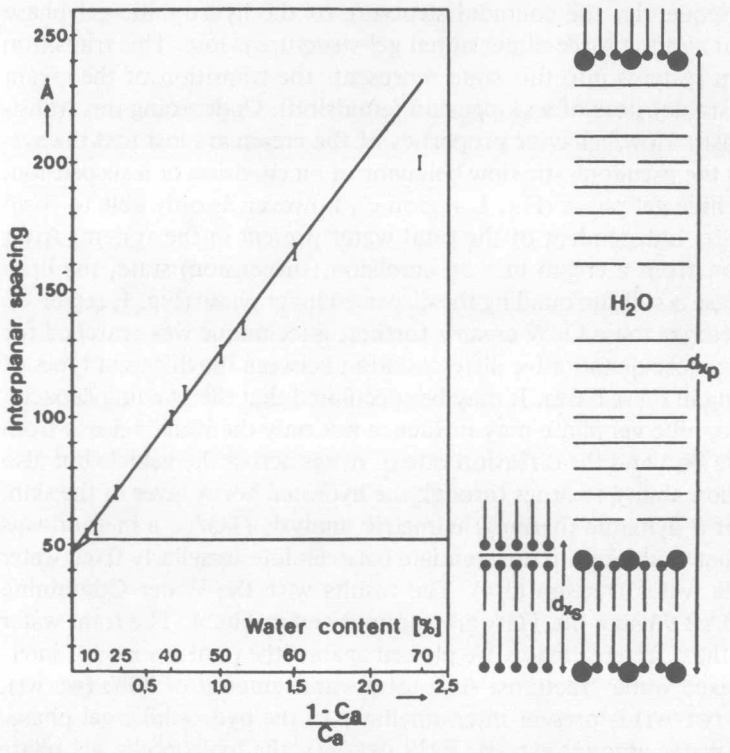

Figure 3 Swelling behavior of Emulsifying Wax DAB 9 with water. C_a, weight fraction of surfactant; $1 - C_a$, weight fraction of water; d_{xs}, interplanar spacings of cetostearylalcohol semihydrate (lipophilic) gel; d_{xp}, interplanar spacings of the hydrophilic gel phase.