Drug Development and Industrial Pharmacy, 26(8), 809–820 (2000)

REVIEW ARTICLE

Monoolein: A Review of the Pharmaceutical Applications

Adriana Ganem-Quintanar,[1,*] David Quintanar-Guerrero,[1] and Pierre Buri[2,3]

[1]*FES-Cuautitlán, Universidad Nacional Autónoma de México, Av. 1o. de Mayo s/n, (Campo 1), Cuautitlán Izcalli, Mexico*
[2]*Pharmapeptides, Centre Interuniversitaire de Recherche et d'Enseignement, 74166 Archamps, France*
[3]*Section de Pharmacie, Université de Genève, Quai Ernest-Ansermet 30, 1211 Genève 4, Suisse*

Key Words: *Absorption enhancer; Drug delivery system; Emulsifier; Glyceryl monooleate; Monoglyceride polymorphism; Monoolein; Pharmaceutical carrier.*

INTRODUCTION

Although monoolein is a well-known molecule commonly used as an emulsifying agent and as a food additive since the 1950s, its potential applicability in the pharmaceutical industry has not been considered in great detail. Recently, there has been a flurry of activity concerned with the possibility of using monoolein as a material for different pharmaceutical applications. The explosion of interest in this field is evidenced by an increase in the number of publications in the area (1).

Figure 1 shows the percentage of consulted references of monoolein versus publication year. It is important to point out that only articles falling in the pharmaceutical area were considered when creating this graphic. Between 1978 and 1987, monoolein was used mainly as an absorption enhancer in combination with bile salts and as an emulsifier. It was in 1984 that monoolein was first proposed as a biocompatible encapsulating and controlled-release material; since then, there have been many diverse applications, and new uses have been proposed, particularly in the last seven years. It should be noted that these applications have been possible because of the increased understanding of the physicochemical properties of monoolein.

In this report, we focus on the application of monoolein in the pharmaceutical area. The ability of monoolein to serve as an emulsifier and permeation enhancer is reviewed. We are also particularly interested in the potential use of monoolein as a drug delivery system for different administration routes.

DEFINITIONS AND PROPERTIES

Monoolein, or glyceryl monooleate, is a mixture of the glycerides of oleic acid and other fatty acids, consisting

* To whom correspondence should be addressed. Río Pánuco 38, Colinas del Lago, Cuautitlán Izcalli, 54744, E. M., México. Telephone: (525) 51.75.30.32.Fax: (525) 58.73.2.73. E-mail: quintana@servidor.unam.mx.

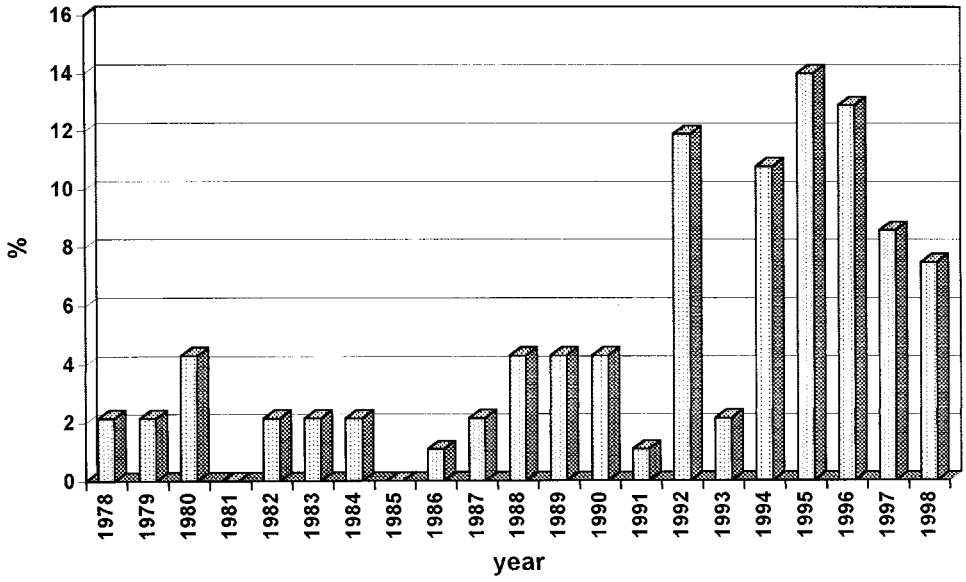

Figure 1. Monoolein publications related to the pharmaceutical field ($n = 93$).

mainly of the monooleate. The acyl chain (oleic acid) is attached to the glycerol backbone by an ester bond (Fig. 2). The two remaining carbons of the glycerol have active hydroxyl groups, giving polar characteristics to this portion of the molecule. The glycerol moiety may form hydrogen bonds with water in an aqueous environment and is commonly referred to as the head group. The hydrocarbon chain gives hydrophobic characteristics to monoolein and is often termed the tail (2–7).

Monoolein can be produced by the direct esterification of fatty acids, chiefly oleic acid and glycerol, or by the glycerolysis (transesterification) of refined vegetable oils, such as erucic canola oil or sunflower oil (8). Commercially available, monoolein may be obtained in two forms, a mixed glyceride form (referred to simply as monoolein) or as distilled monoolein; the latter is preferred for pharmaceutical applications because of its high purity. Monoolein can be mixed with 5% of an anionic surfactant; this mixture is called self-emulsifying grade monoolein. This form is generally used as a primary emulsifier for oil-in-water systems.

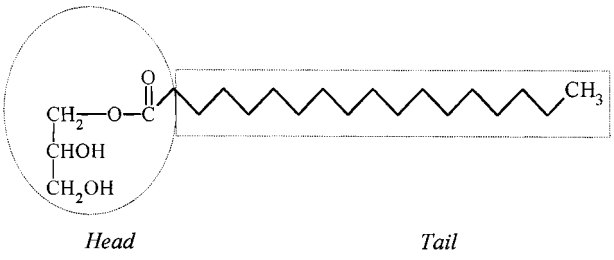

Figure 2. Structural formula of monoolein (for pure material).

Monoolein occurs as a waxy yellow paste with a characteristic odor. It swells in water, giving rise to several lyotropic liquid crystalline structures. From a pharmaceutical standpoint, the phase behavior of the system shows a number of interesting properties. Some phases may be in equilibrium with excess water solutions, and temperature-induced transitions occur between phases of different rheology. Monoolein is a nontoxic, biodegradable, and biocompatible material classified as GRAS (generally recognized as safe), and it is included in the FDA *Inactive Ingredients Guide* and in nonparenteral medicines licensed in the United Kingdom. Its biodegradability comes from the fact that monoolein is subject to lipolysis due to diverse kinds of esterase activity in different tissues (5–10). Other typical properties of monoolein are summarized in Table 1.

MONOOLEIN PHASE BEHAVIOR

In this section, we briefly describe the mesomorphic phases observed with monoolein. We consider this aspect important in making more comprehensible the potential pharmaceutical applications of this lipid.

A common feature of lipids is the existence of a temperature-dependent phase transition. Below the transition

Table 1

Typical Properties of Monoolein

Chemical name	9-Octadecenoic acid (Z)-monoester with 1,2,3-propanetriol
Synonyms	Glycerol-1-oleate, glycerol oleate, glyceryl monooleate, monolein, α-monoolein glycerol
Commercial names	Aldo MO, Arlacel 186, Atlas G-695, Cithrol GMO N/E, Hodag GMO, Myverol 18-99, Priolube 1408, Rylo NG15, Tegin
Empirical formula	$C_{21}H_{40}O_4$ (M_w = 356.55 for pure material)
Acid value	<20
Boiling point	238°C–240°C
Density	0.94 g/cm^3
Flash point	216°C
Free glycerin	≤5.0% (≤1% for distilled)
HLB	3–4
Iodine number	90–100
Melting point	35°C–37°C (36°C for the pure form)
Monoester content	>90% (for the distilled)
Refractive index	1.4626
Saponification value	160–170
Soap content	≅ 0.5%
Solubility	Practically insoluble in water (≅10^{-6} M), soluble in chloroform, ethanol, ether, mineral oil, and vegetable oils
Water content	≤1%

Source: From Refs. 9, 11, and 12.

temperature, lipids exist in a ''gel'' state. An increase in temperature results in the transition to a fluidlike state (liquid crystalline state) similar to the fusion of a crystalline solid; however, when a given lipid molecule is heated, instead of melting directly into an isotropic liquid, it may pass through intermediate states called mesophases or liquid crystals. Such molecules undergo thermotropic mesomorphism. In addition, certain molecules may be induced to form liquid crystals by the addition of a second chemical component, for instance, a solvent such as water (lyotropic mesomorphism) (13).

The ability to exist in several different phases is an important property of pure lipids and lipid mixtures; it depends on temperature, hydration, and lipid class. In general, monoglycerides exhibit different phase behaviors when they are exposed to water (see Fig. 3) (14).

Of these, the most commonly encountered is the spherical micelle; however, this is only one of many aggregate types formed. One also finds reverse micelles, with water in the interior (L_2), as well as liquid crystalline

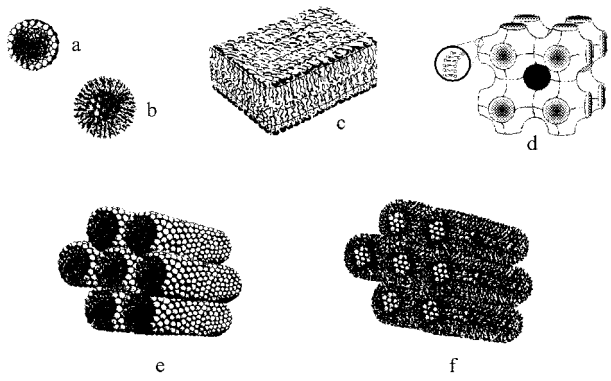

Figure 3. Polymorphic phases available to hydrated liquid crystalline lipids: (a) micellar; (b) inverted miellar; (c) lamellar (Lα); (d) cubic; (e) hexagonal (H_I); (f) inverted hexagonal (H_{II}).

structures such as the hexagonal phases (H_I and H_{II}). The lamellar phase structure (L_α), the originator of liposomes, is also commonly found in polar lipid systems. A less well known liquid crystalline phase is the cubic phase (G and D) (12).

When placed in a water solution, monoolein gives rise to several of these phases, with one-, two-, and three-dimensional periodicity, such as the lamellar, inverted hexagonal, and bicontinuous cubic phases, under rather easily accessible temperature and pressure conditions (6,15–18). Each of these phases can have different pharmaceutical importance.

The phase diagram (Fig. 4) shows that, at 37°C (pure monoolein melts at 36°C) and in the presence of a small

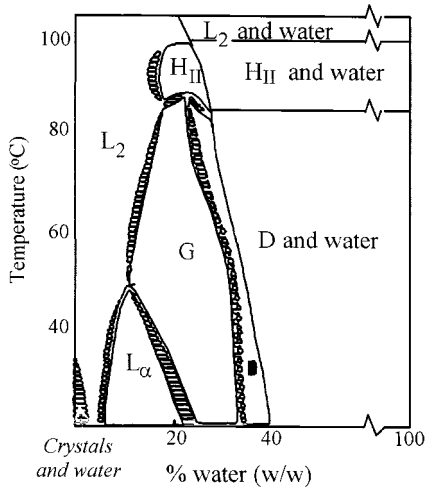

Figure 4. Binary phase diagram of the monoolein-water system. (From Refs. 3, 7, 12, 16, and 20.)

amount of water, monoolein forms reversed micelles (L_2) characterized by an oily texture. Adding more water, a mucouslike system is formed that corresponds to the lamellar phase (L_α) (7,12,19). A large isotropic phase region dominates when more water is added (~20–40%). This phase, known as the cubic phase, is characterized by a high viscosity and, in fact, consists primarily of two cubic phases with similar structures, the cubic phase of the type G, also known as Q^{230} (gyroid), and the cubic phase D or Q^{224} (diamond), although the structural similarity of these phases is such that in practice the two are usually considered to be equivalent (3,16,20–31). At high water content (>40 %), the cubic phase D is in equilibrium with essentially pure water (5,12,25,30).

The cubic phase (Fig. 3d) is said to be *bicontinuous* since it consists of a curved bilayer extending in three dimensions, separating two congruent water channel networks. The water pore diameter is about 5 nm when the cubic phase is fully swollen. The presence of a lipid and an aqueous domain gives special properties to the cubic phase, such as the ability to solubilize both water- and lipid-soluble compounds, as well as amphiphilic substances (12,32,33). If one intends to use the monoolein-water system for drug delivery, it is crucial to gain insight into how a third substance (e.g., a drug) influences the phase behavior of the system (34). Many drugs can be incorporated, up to 10–15%, in the cubic phase, but that depends, of course, on the type of drug (2). Monoolein also forms a liquid sponge phase, a bicontinuous lipid-water system, when solvents like propylene glycol or poly(ethylene glycol) are added to the monoolein-water system (35).

PHARMACEUTICAL USES OF MONOOLEIN

The applications of monoolein in the pharmaceutical area have mainly centered on the design of drug products. The special behavior of this lipid can either represent a solution for the development of new drug delivery systems or be an interesting alternative to those already in use. The growing interest in this monoglyceride results in the commercialization of different products using monoolein as a drug carrier material.

In the pharmaceutical field, the applications of monoolein can be classified as follows: (*a*) emulsifier, (*b*) solubilizer, (*c*) absorption enhancer, (*d*) oral drug delivery system, (*e*) parenteral drug delivery system, (*f*) vaginal drug delivery system, (*g*) periodontal drug delivery system, (*h*) colloidal carrier system, (*i*) storage system for the protection of macromolecules susceptible to degradation, (*j*) bioadhesive, and (*k*) others, such as a membrane and polymorphic lipid model for the determination of lipid bilayer/water partition coefficient and electrochemical biosensors.

Emulsifier

Due to its amphiphilic character, monoolein has been classified as a nonionic surfactant. It has been used as an emulsifying agent for water-in-oil emulsions and microemulsions and in cosmetic and pharmaceutical topical formulations. The self-emulsifying grade is used as a primary emulsifier for oil-in-water systems (9,36–39). When used in hydrocarbon ointment bases, it has shown water-absorbing and water-retaining capacities, as well as the ability to change the rheological properties of ointments (40,41). Furthermore, monoolein could be attractive for formulating dermical preparations because of their release properties and substantivity (39). Recently, monoolein has been proposed as a cosurfactant for the development of an injectable oil-in-water emulsion containing lipophilic antioxidants (42).

Solubilizer

In studies of fat digestion, it has been well established that monoolein mixed with bile salts forms a mixed micellar phase, which improves fat solubilization (43,44). The molecular arrangement of the particles present in the isotropic part of the monoolein/bile salt map is qualitatively the same as that in phosphatidylcholine/bile salt systems (45). Thus, both monoolein and lecithin enhance solubilization of solutes in bile salt solutions, having physicochemical effects principally on solubility, wetting, and dissolution of drugs. Luner et al. (46) showed that the addition of increasing amounts of monoolein to glycocholate solutions resulted in a linear increase in the solubility of gemfibrozil. Another interesting study using the solubilizer properties of monoolein/bile salt solutions was carried out by Kararli and Gupta (47). These authors stated that it is possible to increase the solubilization of a leucotriene-D_4 in mixed micellar solutions of taurocholate plus monoolein. The effect of monoolein on the surfactant solution was to increase the size of the mixed micelles. These data of enhanced solubility from monoolein/bile salts can be of use in the formulation of physiologically relevant dissolution media. In an interesting recent study, Barauskas et al. (48) studied the solubilization of ubiquinone-10, showing that a content below 0.5 wt% has no effect on the monoolein bilayer thickness

and the swelling behavior of phases, and then the coenzyme seems to be totally dissolved in the monoolein.

Absorption Enhancer

The mixed micellar phases formed between monoolein and bile salt solutions have also been proposed as potential modifiers of the intestinal absorption of lipophilic, hydrophilic, and macromolecular drugs (49). Work at the University of Kyoto has shown that the intestinal absorption of poorly absorbed drugs such as gentamicin or streptomycin (50,51), heparin (52,53), and a macromolecular bleomycin dextran sulfate complex (55) was greatly enhanced in the presence of monoolein/bile salt mixed micelles. These studies suggested that the most important component responsible for the marked enhancement across the intestinal membrane is apparently not the bile salt, but monoolein. Thus, monoolein is considered a low-melting fusogenic lipid that might produce a reversible increase in the fluidity of the lipid bilayer (55–58).

The increase in large intestinal absorption was found to be much greater than that in the small intestine. Furthermore, the administration of drugs in mixed micelle powder form is, in practical terms, more convenient by rectal administration, for which mixed micelles are not expected to be diluted extensively. Consequently, it was found that colorectal administration with mixed micelles was more advantageous for the absorption of poorly absorbable drugs than oral administration (49,50,52,59). This has been confirmed recently for the absorption of human calcitonin across the rat colon in vivo (60).

Monoolein–bile salt aqueous solutions have also been shown to be capable of promoting the intestinal absorption of poorly absorbed drugs incorporated in oily, liposomal (56), and emulsion (58) formulations. In this sense, Balandraud et al. (61) have shown that the oral bioavailability of cyclosporin A in rats was improved significantly (with low variability) using an aqueous micellar solution containing tauroursodeoxycholate and monoolein. Improved nasal absorption has also been observed when monoolein is used as an adjuvant. Kararli et al. (62) showed that emulsion formulations containing oleic acid, monoolein, and sodium taurocholate (or Tween 80) enhanced the nasal absorption of a renin inhibitor. The mechanism of drug transport was related to an increase in membrane fluidity brought about by the interaction of oleic acid and monoolein with the nasal membrane. Furthermore, it was shown that the use of lipids in mixed micellar solutions may reduce the mucosal damage caused by bile salt micelles alone.

Monoolein was also shown to be effective as a transdermal enhancer (63). In enhancing the flux of nitrendipine across human skin, the authors found that monoolein was the most effective enhancer among a series of enhancers, such as oleic acid, lauryl alcohol, L-menthol, Transcutol®, Labrasol®, Tween 80, Tween 20, and *N*-methyl-2-pyrrolidone. Monoolein appears to act via the same mechanism as oleic acid, causing a temporary and reversible disruption of the lamellar structure of lipid bilayers in the stratum corneum and in this way increasing intercellular lipid fluidity.

Oral Drug Delivery System

Since the appearance of the first patent in 1984 (64) proposing amphiphilic substances as interesting candidates for matrices or barriers in controlled-release preparations, monoolein has been considered an attractive basis for the development of these systems. A matrix device, as the name implies, consists of a drug dispersed homogeneously throughout a material that generally is polymeric in nature. Carboxymethylcellulose, hydroxypropylmethylcellulose, ethylcellulose, methylcellulose, polyvinyl alcohol, polyvinylpyrrolidone and polyethylene glycols are some of the more commonly used controlled-release polymers (65). Monoolein behaves in a manner similar to certain polymers in that, as mentioned above, in excess water it swells and forms a physically stable viscous gel (the highly ordered cubic phase) that will release a dissolved or dispersed drug by slow diffusion (4,8). Thus, monoolein can be an interesting alternative to polymer systems. The drug/monoolein mixture could be melt filled into hard capsules and then cooled. Once in contact with gastrointestinal fluids at body temperature, the monoglyceride transforms into the cubic phase after dissolution of the gelatin capsule (66,67).

Some typical advantages and disadvantages of the use of monoolein instead of polymers, which are applicable to other systems reviewed in this report, are summarized next (4,6,8,66–71). Monoolein has the following advantages: (*a*) it is well characterized; (*b*) it is easy to design and formulate; (*c*) it is biocompatible and biodegradable; (*d*) there is an absence of toxic impurities such as residual monomers, catalysts, and initiators; (*e*) the melts have, in contrast to polymer melts, a low melt viscosity, thus obviating the need for organic solvents for solubilization; (*f*) because of its amphiphilic nature, both hydrophilic and lipophilic drugs can be incorporated and released; (*g*) the drug can be dissolved in the cubic phase, or if the amount exceeds its solubility in the cubic phase, it often forms a dispersion in the cubic phase; (*h*) the ionic

strength and pH of the buffer media do not affect monoglyceride swelling considerably; (*i*) the drug release could be controlled by varying the surface-to-volume ratio, the drug loading, and the water content of the lipid and by the addition of salt, glycerol, propylene glycol, or any similar amphiphilic substance of low molecular weight.

The disadvantages of monoolein are the following: (*a*) it is necessary (especially for amphiphilic drugs) to build drug(s)/monoolein/solvent phase diagrams to know the influence of the drug(s) on the phase behavior and the regions of greatest physical stability; (*b*) it could be sensitive to interactions with food components or gastrointestinal fluids, and bile salts particularly can provoke the micellization or emulsification of monoolein; (*c*) the presence of surface-active molecules can affect the integrity of the matrix; (*d*) there is incomplete release of certain hydrophilic drugs by binding of the drug molecules with the cubic phase; (*e*) there is a potential for sedimentation of drug crystals during preparation; and (*f*) the stiffness of the cubic phase makes it difficult to handle.

It should be noted that the release mechanism from monoolein-based systems is associated closely with the diffusional exchange of water from the external media of the matrix and drug and water from the interior phase, being second-order swelling kinetics. This exchange exhibits typical square-root dependent drug release, at least during the initial release phase (4,66,72,73).

Parenteral Drug Delivery System

The cubic phase reveals great flexibility since drugs of very different polarity and size may be incorporated. Of special interest is its ability to solubilize peptides and proteins. The reason for the flexibility of the system is its amphiphilic nature since the cubic phase roughly consists of equal amounts of lipid and water. The bilayer structure gives rise to a large interfacial area ($\sim$400 m^2/g as the cubic phase), which should promote the incorporation of amphiphilic substances. Considering these advantages, the cubic phase may be used as a parenteral delivery system, as has been proposed by Ericsson et al. (5,74). These authors showed that the intramuscular and subcutaneous administration to rabbits of desmopressin or somatostatin encapsulated in a cubic phase produced a constant desmopressinlike and somatostatinlike immunoreactivity over 6 hr.

A serious drawback to using a monoolein system based in the phase cubic is its stiffness, which makes it almost impossible to inject. Two proposals have been made to overcome this problem (75–78). The first is the addition of a third component (a drug or an injectable solvent); after a portion of the drug is released or the solvent is diffused out under physiological conditions, the high viscosity cubic phase is formed. The second is the formation of an L_2 phase by adding a vegetable or animal oil to the hydrated monoolein (64). Both approaches have been successful for the encapsulation and sustained release of biologically active materials such as lysozyme, hydrocortisone, benzylpenicillin, some enzymes, and the like.

One important aspect of the use of monoolein as a safe parenteral material is the necessity to confirm its biological tolerance. Although monoolein disappears after in vivo subcutaneous and intramuscular injection, principally by lipase activity (10), its nonirritant effect on the tissues has not been entirely confirmed and recently even has been refuted (80). Further studies are therefore necessary to clarify this issue.

Periodontal Drug Delivery System

The special swelling characteristics of monoolein, as well as its biodegradability by the action of different kinds of esterases, make this substance the ideal candidate for the administration of drugs via the periodontal pocket. Taking advantage of the capacity of monoolein to form different liquid crystalline phases, a ''dental gel'' with a mixture of monoolein and a vegetable oil was prepared for the administration of active agents (such as antiseptics, antibiotics, antifungal agents, anti-inflammatory drugs, antiplaque agents, and anesthetics) used in the treatment of periodontal diseases. Elyzol® is a dental gel of this type and is manufactured and marketed by Dumex-Alpharma A/S in several European countries and uses metronidazole benzoate as the active ingredient. The fluid gel may be administered by syringe, but then on contact with the water of the gingival fluid, it undergoes an in situ transformation to a semisolid system, presumably a reverse hexagonal liquid crystalline matrix. The system has been shown to adhere to the mucosa and fit well in the dental pocket, allowing, in addition, controlled release of the drug. Furthermore, the gel has an advantage over the nonbiodegradable polymer carriers in that it may be easily degraded by the action of the body's own lipases or by the enzymes liberated by the bacteria found in periodontal pockets. The gel is then converted to oleic acid and glycerol, which can be easily flushed out of the pocket and disposed of via the saliva without the necessity for mechanical removal (80,81).

Vaginal Drug Delivery System

Recently, Geraghty et al. (82,83) investigated the potential use of a monoolein/water liquid crystalline gel for vaginal delivery of antimuscarinic drugs. They found that the release of the drugs in vitro was sustained over a period of about 18 hr and followed square-root-of-time kinetics, indicating that the rate of release was diffusion controlled. The release profiles have also been found to be dependent on the solubility of the drug in the lipid base and the extent of partitioning into the lipid bilayer. Subsequent work (18) detailing in vivo monoolein retention assessment by gamma scintigraphy showed that the gels were retained in the vaginal canals for a minimum of 6 hr. The gels did not produce signs of mucosal irritation or sensitization and appeared to have been degraded by enzymes present in the vaginal cavity after a 24-hr period. No trace of gel or activity was found on the fur or on the trays of the animals. Gel retention was attributed more to their high viscosity than to their bioadhesive properties.

It is important to mention that an intravaginal product commercialized as Provagin® was designed using monoolein as a matrix support for micronized natural progesterone. The aim of Provagin is to prepare the uterine mucosa for implantation of an embryo after in vitro fertilization.

Colloidal Carrier Systems: Cubosome and Hexosome Formulations

Cubosomes® and Hexosomes™ are submicron dispersions of particles of a cubic or reversed hexagonal lipid-water phase prepared by the mechanical dispersion of the lipid and the addition of amphiphilic molecules, such as block copolymers (e.g., pluronics), that provide stearic stabilization (particles in the range 1–100 μm are formed by mild agitation of the cubic phase, while submicronic particles are formed using high-pressure homogenization). These phases have been shown to be useful in drug delivery, particularly due to their bioadhesive properties, their characteristics as sustained-release delivery systems, and their ability to protect peptide drugs from degradation. It is important to mention that Cubosomes show a structural organization identical to that found in biomembranes (84,85).

The use of Cubosome formulations for intravenous administration of somatostatin was reported by Engström et al. (85). The authors found that somatostatin remained in the circulation much longer when administered in Cubosomes than when administered as an intravenous bolus injection. Thus, Cubosomes may be a promising alternative to liposomes and conventional emulsions due to their unique properties, such as the ability to circulate in the bloodstream for many hours. This effect is attributed to their behaving like ''stealth'' liposomes due to their long, protruding hydrophilic ethylene oxide chains. The Cubosome dispersion also offers the possibility to incorporate a greater variety of drugs in comparison to liposomes and emulsions. Moreover, in the Cubosome, the lipid bilayer extends through the whole particle, in contrast to a liposome, which has a relatively large aqueous interior (12,85).

However, in spite of these optimistic results, further investigations are still required (86) to elucidate the stability of Cubosomes and their use as intravenous delivery systems.

Storage System for the Protection of Macromolecules Susceptible to Degradation

Cubic phases are unique in their ability to accommodate proteins. Ericsson et al. (87) determined that the cubic phase was able to incorporate globular proteins with molecular weights between 14 and 150 kDa, and Larsson (25) examined the ternary lipid-protein-water phase diagrams for a wide range of globular proteins with molecular weights between 5000 and 150,000, all of which formed cubic phases. Razumas (88) found that enzymes with molecular weights up to 590 kDa can be entrapped and stabilized. It was proposed that water-soluble protein molecules are located in the water channel systems of the cubic structure (87,89), whereas lipophilic proteins are integrated into the lipid bilayer (84). A remarkable feature in the monoolein-protein-water systems is that large amounts of protein in native conformations can be incorporated without ionic interaction with the lipid bilayer (88).

The particular structure of the cubic phase may function as a protector medium for proteins. For example, it was observed that the high viscosity of monoolein gels could render the insulin molecule immobile and thus enhance its stability (90,91). A similar effect was observed for cefazolin and glucose oxidase, formulated in the monoolein cubic phase, in which apparently the reduction of the mobility of water due to the highly structured nature of the gel protects the drug from chemical degradation (92–94). Protection against enzymatic degradation was also observed for small peptides, such as 1-deamino-8-d-arginine vasopressin and lysine vasopressin, when

incorporated in the cubic phase (95). Desmopressin, lysine vasopressin, somatostatin, and the renin inhibitor were protected against enzymatic cleavage in simulated intestinal fluid when formulated in the cubic phase (5). In this study, it was observed that the degradation rates were mainly dependent on the release rates of the peptide from the phase to the surface during the experiment. In the same way, diffusion of the enzyme (chymotrypsin) into the cubic phase was negligible due to its large size compared to the water pores in the cubic phase.

A rapid proteolytic degradation and a risk of inmune response limit the use of exogenous enzymes in the treatment of enzyme deficiency diseases. To overcome these problems, model hydrophilic and transmembrane enzymes were formulated in a monoolein lamellar phase that converts in situ into a cubic phase (76,77). Results showed that the immobilized enzymes inside the matrix were protected from proteolytic enzymes in the surrounding media, and that the matrix slowly biodegraded by circulating esterase enzymes, obviating the need for surgical removal.

Different proteins and peptidelike drugs, such as casein (96), human calcitonin (60), heparin (52,53,59), leuprolide (97), insulin (90,91), leucotriene-D_4 (98), somatostatin (74), and A-gliadin (99), and lysozyme (89) and cefazolin (100) have been reported to form monoolein cubic phases.

Bioadhesive

Monoolein has some molecular characteristics similar to those observed in polymeric materials used as bioadhesives. It is an amphiphilic molecule with secondary bond-forming capacity due to the presence of hydroxyl and ester groups and with surface-active properties. It has a flexible hydrocarbon chain and takes up water-forming gel phases, which apparently remain in confined areas such as the periodontal pocket (as mention above). Based on these assumptions, Engström et al. (101) studied the adhesive force between lingual and sublingual mucosa and the cubic and lamellar phases formed with monoolein. They classified the monoolein as having moderate to excellent bioadhesive properties. Furthermore, these authors demonstrated that monoolein-based systems adhered to human gum for more than 7 hr. On the other hand, Geraghty et al. (18) showed that monoolein gels bind more strongly to a dry Perspex surface than to moist mucosal tissue and were weaker bioadhesives than Carbopol 934P and sodium alginate. It was concluded that interpenetration was not the mechanism of bioadhesion, but that secondary chemical bonds, such as van der Waals forces, were responsible.

In a more recent work, Nielsen et al. (102) seem to clarify some aspects on the monoolein bioadhesivity. Using a ''flushing'' bioadhesion test and an in vitro tensiometric method on rabbit jejunum, they demonstrated the mucoadhesive properties of monoolein. These authors showed that the unswollen monoglyceride has the greatest mucoadhesion, followed by the partly swollen lamellar phase and the fully swollen cubic phase. This last phase is mucoadhesive when formed on wet mucosa. The proposed mechanism of mucoadhesion is unspecific and probably involves the dehydration of the mucosa.

Other Uses

Monoolein has been used for several other applications in different areas related to the pharmaceutical field. Monoolein can be an excellent model of bilayer membranes to study the passage of substances under different conditions or to determine the transport mechanism. For example, Sesta and D'Aprano (103) used monoolein bilayers to investigate the efficiency of synthetic macrocyclic substances as carriers for the alkali and the alkaline earth ions by conductimetric measurements. Recently Barth et al. (104) analyzed the change of the rate constants of the ion carrier valinomycin as a consequence of the adsorption of a dipolar substance to the membrane/water interface of monoolein membranes. This application can be used to study the in vitro interaction of drugs with lipid bilayers (105) and to determine the lipid bilayer/water partition coefficient (106) or to evaluate the mechanism of action of skin penetration enhancers such as Azone® (107).

The cubic phase of monoolein has been also proposed for electroanalytical applications to construct enzyme-based biosensors. The idea was used to construct and investigate the performance of amperometric β-D-glucose and L-lactate and pH-sensitive urea and creatinine bioelectrodes based on glucose oxidase, lactate oxidase, urease, and creatinine deiminase (108).

Finally, the aqueous channels of the cubic crystalline phase have become useful in protein crystallization (e.g., bacteriorhodopsin) (109).

CONCLUSIONS

A significant number of publications present monoolein as an attractive material for the development of dif-

ferent pharmaceutical systems. Its nature and physicochemical behavior make it an interesting alternative in relation to other conventionally used materials such as polymers. The most significant advantages of monoolein are probably its solubilizing capability, rheological behavior, and low toxicity.

Monoolein has been shown to be a versatile material since it is possible to include it in very different systems. However, before its use as a pharmaceutical ingredient, further investigations are required, focusing on its colloidal stability, oral bioavailability, parenteral toxicity, and bioadhesive properties.

The presence on the market of commercialized products that include monoolein as a basis of the formulation shows the increased interest of the pharmaceutical industry in investing in the development and safety testing of commercial preparations, suggesting a promising future for this material.

REFERENCES

1. J. Briggs and M. Caffrey, The temperature-composition phase diagram and mesophase structure characterization of monopentadecenoin in water, Biophys. J., 67, 1594–1602 (1994).
2. J. Morant and H. Ruppaner (Eds.), Compendium suisse de médicaments, Basler Zeitung, Bale, 1995, p. 600.
3. V. Luzzati, P. Mariani, and T. Gulik-Krzywicki, The cubic phases of liquid-containing systems: physical structure and biological implications, in *Les Houches Workshop, Physics of Amphiphilic Layers*, Springer-Verlag, Berlin, 1987, pp. 131–137.
4. S. Engström, K. Larsson, and B. Lindman, Liquid crystalline phases as delivery systems for drugs. I. Basic principles, Proc. Int. Symp. Controlled Release Bioact. Mater., 15, 105–106 (1988).
5. B. Ericsson, P. O. Ericsson, J. E. Löfroth, and S. Engström, Cubic phases as delivery systems for peptide drugs, Am. Chem. Soc. Symp. Ser., 469, 251–265 (1991).
6. S. Engström, L. Lindahl, R. Wallin, and J. Engblom, A study of polar lipid drug carrier systems undergoing a thermoreversible lamellar-to-cubic phase transition, Int. J. Pharm., 86, 137–145 (1992).
7. E. Boyle and J. B. German, Monoglycerides in membrane systems, Crit. Rev. Food Sci. Nutr., 36, 785–805 (1996).
8. M. Longer, P. Tyle, and J. W. Mauger, A cubic-phase oral drug delivery system for controlled release of AG337, Drug Dev. Ind. Pharm, 22, 603–608 (1996).
9. A. Wade and P. J. Weller (Eds.), *Handbook of Pharmaceutical Excipients*, 2nd ed., 1994, pp. 207–208.
10. L. Appel, K. Engle, J. Jensen, L. Rajewski, and G. Zentner, An in vitro model to mimic in vivo subcutaneous monoolein degradation, Pharm. Res., 11, S-217 (1994).
11. U.S. Pharmacopeial Convention, *The United States Pharmacopeia 22/National Formulary 17*, Author, Rockville, MD, 1990, p. 2250.
12. S. Engström, Drug delivery from cubic and other lipid-water phases, Lipid Technol., 2, 42–45 (1990).
13. F. B. Rosevear, The microscopy of the liquid crystalline neat and middle phases of soaps and synthetic detergents, J. Am. Oil Chem. Soc., 31, 628–639 (1954).
14. G. Y. Brokaw and W. C. Lyman, The behavior of distilled monoglycerides in the presence of water, J. Am. Oil Chem. Soc., 35, 49–53 (1958).
15. E. S. Lutton, Phase behavior of aqueous systems of monoglycerides, J. Am. Oil Chem. Soc., 42, 1068–1070 (1965).
16. V. Luzzati, P. Mariani, and H. Delacroix, X-ray crystallography at macromolecular resolution: a solution of the phase problem, Makromol. Chem., Macromol. Symp., 15, 1–17 (1988).
17. C. Czeslik, R. Winter, G. Rapp, and K. Bartels, Temperature- and pressure-dependent phase behavior of monoacylglycerides monoolein and monoelaidin, Biophys. J., 68, 1423–1429 (1995).
18. P. B. Geraghty, D. Attwood, J. H. Collett, H. Sharma, and Y. Dandiker, An investigation of the parameters influencing the bioadhesive properties of Myverol 18-99/water gels, Biomaterials, 18, 63–67 (1997).
19. A. Nilsson, A. Holmgren, and G. Lindblom, FTIR study of lamellar and reversed micellar phases in the monooleoylglycerol/water system, Chem. Phys. Lip., 69, 219–227 (1994).
20. K. Larsson, Two cubic phases in monoolein-water system, Nature, 304, 664 (1983).
21. W. Longley and T. J. McIntosh, A bicontinuous tetrahedral structure in a liquid-crystalline lipid, Nature, 303, 612–614 (1983).
22. S. T. Hyde and S. Andersson, A cubic structure consisting of a lipid bilayer forming an infinite periodic minimum surface of the gyroid type in the glycerol-monooleatewater system, Z. Kristallogr., 168, 213–219 (1984).
23. M. Caffrey, Kinetics and mechanism of transitions involving the lamellar, cubic, inverted hexagonal, and fluid isotropic phases of hydrated monoacylglycerides monitored by time-resolved X-ray diffraction, Biochem., 26, 6349–6363 (1987).
24. P. Mariani, V. Luzzati, and H. Delacroix, Cubic phases of lipid-containing systems. Structure analysis and biological implications, J. Mol. Biol., 204, 165–189 (1988).
25. K. Larsson, Cubic lipid-water phases: structures and biomembrane aspects, J. Phys. Chem., 93, 7304–7314 (1989).

26. K. Fontell, Cubic phases in surfactant and surfactant-like lipid systems, Colloid Polym. Sci., 268, 264–285 (1990).
27. T. Landh, Phase behavior in the system pine oil monoglycerides–poloxamer 407–water at 20°C, J. Phys. Chem., 98, 8453–8467 (1994).
28. K. Larsson, K. Fontell, and N. Krog, Structural relationships between lamellar, cubic and hexagonal phases in monoglyceride-water systems. Possibility of cubic structures in biological systems, Chem. Phys. Lipids, 27, 321–328 (1980).
29. W. Buchheim and K. Larsson, Cubic lipid-protein-water phases, J. Colloid Interface Sci., 117, 582 (1987).
30. R. He and D. Q. M. Craig, Low-frequency dielectric investigations into the phase behavior of glyceryl monoolein/water systems, J. Phys. Chem. B, 102, 1781–1786 (1998).
31. R. He and D. Q. M. Craig, Identification of thermotropic phase transitions of glyceryl monoolein/water systems by low-frequency dielectric spectroscopy, Int. J. Pharm., 169, 131–141 (1998).
32. G. Lindblom and L. Rilfors, Cubic phases and isotropic structures formed by membrane lipids—possible biological relevance, Biochim. Biophys. Acta, 988, 221–256 (1989).
33. G. Lindblom, K. Larsson, L. Johansson, K. Fontell, and S. Forsén, The cubic phase of monoglyceride-water systems. Arguments for a structure based upon lamellar bilayer units, J. Am. Chem. Soc., 101, 5465–5470 (1979).
34. S. Engström and L. Engström, Phase behaviour of the lidocaine-monoolein-water system, Int. J. Pharm., 79, 113–122 (1992).
35. K. Alfons and S. Engstrom, Drug compatibility with the sponge phases formed by monoolein, water, and propylene glycol or poly(ethylene gycol), J. Pharm. Sci., 87, 1527–1530 (1998).
36. A. Jayakrishnan, K. Kalaiarasi, and D. O. Shah, Microemulsions: evolving technology for cosmetic applications, J. Soc. Cosmet. Chem., 34, 335–350 (1983).
37. G. M. Eccleston, Emulsion, in *Encyclopaedia of Pharmaceutical Technology*, Vol. 5 (J. Swarbrick and J. C. Boylan, Eds.), Marcel Dekker, New York, 1992, pp. 137–188.
38. C. Henry, Monoglycerides: the universal emulsifier, Cereal Foods World, 40, 734–736 (1995).
39. N. Sadrzadeh, H. Yu, and G. Zografi, Interfacial properties in mixtures of lipids and polymers, AAPS Annual Meeting, 239 (1995).
40. I. Eros and E. Ugri-Hunyadvári, Investigation of the rheological characteristics of ointment gels containing emulsifiers and emulsion-type ointments, Cosmetics Toiletries, 94, 67–79 (1979).
41. É. Ugri-Hunyadvári, E. Soós-Csányi, É. Biczók, and Cs. Kovács, Investigation of the emulsifying capacity of glyceril monostearate and -oleate in ointments, Acta Pharm. Hung., 56, 38–45 (1986).
42. R. T. Lyons, Formulation development of an injectable oil-in-water emulsion containing the lipophilic antioxidants (alpha)-tocopherol and β-carotene, AAPS Annual Meeting, 226 (1996).
43. J. S. Patton and M. C. Carey, Watching fat digestion, Science, 204, 145–148 (1979).
44. P. Borel, M. Martigne, M. Senft, P. Garzino, H. Lafont, and D. Lairon, Effect of wheat bran and wheat germ on the intestinal uptake of oleic acid, monoolein, and cholesterol in the rat, J. Nutr. Biochem., 1, 28–33 (1990).
45. R. P. Hjelm, C. Schteingart, A. F. Hofmann, and D. S. Sivia, Form and structure of self-assembling particles in monoolein-bile salt mixtures, J. Phys. Chem., 99, 16395–16406 (1995).
46. P. E. Luner, S. R. Babu, and G. W. Radebaugh, The effects of bile salts and lipids on the physicochemical behavior of gemfibrozil, Pharm. Res., 11, 1755–1760 (1994).
47. T. T. Kararli and V. W. Gupta, Solubilization and dissolution properties of a leucotriene-D_4 antagonist in micellar solutions, J. Pharm. Sci., 81, 483–485 (1992).
48. J. Barauskas, V. Razumas, and T. Nylander, Solubilization of ubiquinone-10 in the lamellar and bicontinuous cubic phases of aqueous monoolein, Chem. Phys. Lipids, 97, 167–179 (1999).
49. S. Muranishi, Modification of intestinal absorption of drugs by lipoidal adjuvants, Pharm. Res., 2, 108–118 (1985).
50. S. Muranishi, N. Muranushi, and H. Sezaki, Improvement of absolute bioavailability of normally poorly absorbed drugs: inducement of the intestinal absorption of streptomycin and gentamycin by lipid-bile salt mixed micelles in rat and rabbit, Int. J. Pharm., 2, 101–111 (1979).
51. N. Muranishi, M. Kinugawa, Y. Nakajima, Sh. Muranishi, and H. Sezaki, Mechanism for the inducement of the intestinal absorption of poorly absorbed drugs by mixed micelles. I. Effects of various lipid-bile salt mixed micelles on the intestinal absorption of streptomycin in rat, Int. J. Pharm., 4, 271–279 (1980).
52. Y. Tokunaga, S. Muranishi, and H. Sezaki, Enhanced intestinal permeability to macromolecules. I. Effect of monoolein-bile salts mixed micelles on the small intestinal absorption of heparin, J. Pharm. Dyn., 1, 28–38 (1978).
53. K. Taniguchi, S. Muranishi, and H. Sezaki, Enhanced intestinal permeability to macromolecules. II. Improvement of the large intestinal absorption of heparin by lipid-surfactant mixed micelles in rat, Int. J. Pharm., 4, 219–228 (1980).
54. H. Yoshikawa, H. Sezaki, and S. Muranishi, Mechanism for selective transfer of bleomycin into lymphatics by a

bifunctional delivery system via the lumen of the large intestine, Int. J. Pharm., 13, 321–332 (1983).
55. N. Muranushi, M. Kinugawa, Y. Nakajima, S. Muranishi, and H. Sezaki, Mechanism for the inducement of the intestinal absorption of poorly absorbed drugs by mixed micelles. I. Effects of various lipid-bile salt mixed micelles on the intestinal absorption of streptomycin in rat, Int. J. Pharm., 4, 271–279 (1980).
56. N. Muranushi, Y. Nakajima, M. Kinugawa, S. Muranishi, and H. Sezaki, Mechanism for the inducement of the intestinal absorption of poorly absorbed drugs by mixed micelles. II. Effect of the incorporation of various lipids on the permeability of liposomal membranes, Int. J. Pharm., 4, 281–290 (1980).
57. C. P. S. Tilcock and D. Fisher, Interactions of glycerol monooleate and dimethylsulphoxide with phospholipids, Biochim. Biophys. Acta, 685, 340–346 (1982).
58. T. T. Kararli, T. E. Needham, M. Griffin, G. Schoenhard, L. J. Ferro, and L. Alcorn, Oral delivery of a renin inhibitor compound using emulsion formulations, Pharm. Res., 9, 888–893 (1992).
59. R. H. Engel and M. J. Fahrenbach, Intestinal absorption of heparin in the rat and gerbil (33422), Proc. Soc. Exp. Biol. Med., 129, 772–777 (1978).
60. J. Hastewell, S. Lynch, R. Fox, I. Williamson, P. Skelton-Stroud, and M. Mackay, Enhancement of human calcitonin absorption across the rat colon in vivo, Int. J. Pharm., 101, 115—120 (1994).
61. P. N. Balandraud, P. E. Quereau, B. F. Caroli, and P. P. Bertault, Effects of tauroursodeoxycholate solutions on cyclosporin A bioavailability in rats, Drug Metab. Dispos., 25, 912–916 (1997).
62. T. T. Kararli, T. E. Needham, G. Schoenhard, D. A. Baron, R. E. Schmidt, B. Katz, and B. Belonio, Enhancement of nasal delivery of a renin inhibitor in the rat using emulsion formulations, Pharm. Res., 9, 1024–1028 (1992).
63. S. A. Giannakou, P. P. Dallas, D. M. Rekkas, and N. H. Choulis, Development and in vitro evaluation of nitrendipine transdermal formulations using experimental design techniques, Int. J. Pharm., 125, 7–15 (1995).
64. S. Engström, K. Larsson, and B. Lindman, Method of preparing controlled-release preparations for biologically active materials, European Patent 0 126 751 (1984).
65. G. M. Jantzen and J. R. Robinson, Sustained- and controlled-release drug delivery systems, in *Modern Pharmaceutics*, Vol. 72 (G. S. Banker and C. T. Rhodes, Eds.), Marcel Dekker, New York, 1996, pp. 575–609.
66. D. M. Wyatt and D. Dorschel, A cubic-phase delivery system composed of glyceryl monooleate and water for sustained release of water-soluble drugs, Pharm. Technol., 116–122 (October 1992).
67. Ch.-M. Chang and R. M. Bodmeier, Effect of dissolution media and additives on the drug release from cubic phase delivery systems, J. Controlled Release, 46, 215–222 (1997).
68. S. A. Abbas and M. Polikandritou, Sustained release from monoolein matrices: effect of pH and bile salt concentration, AAPS Annual Meeting, 286 (1996).
69. Ch.-M. Chang and R. Bodmeier, Binding of drugs to monoglyceride-based drug delivery systems, Int. J. Pharm., 147, 135–142 (1997).
70. S. Engström, T. Landh, and G. Ljunger, The effect of lidocaine on the phase behaviour of the mono-olein/water system, Proc. 5th Int. Conf. Pharm. Technol., 199 (1989).
71. C. M. Chang and R. Bodmeier, Swelling of and drug release from monoglyceride-based drug delivery systems, J. Pharm. Sci., 86, 747–752 (1997).
72. R. Burrows, J. H. Collett, and D. Attwood, The release of drugs from monoglyceride-water liquid crystalline phases, Int. J. Pharm., 111, 283–293 (1994).
73. R. He and D. Q. M. Craig, Characterization of the effects of drug addition on the structure of glyceryl monoolein/water systems using low frequency dielectric spectroscopy, J. Pharm. Sci., 88, 635–639 (1999).
74. B. Ericsson, S. Leander, and M. Ohlin, Liquid crystalline phases as delivery systems for drugs. III: In vivo, Proc. Int. Symp. Controlled Release Bioact. Mater., 15, 382–383 (1988).
75. S. Engström, B. Lindman, and K. Larsson, Method of preparing controlled-release preparations for biologically active materials and resulting compositions, U.S. Patent 5,151,272 (1992).
76. S. Kumar and K. J. Himmelstein, Enzyme immobilization in an injectable, in situ gel-forming system for replacement therapy, AAPS Annual Meeting, 77 (1996).
77. S. Kumar and K. J. Himmelstein, Injectable, self-assembling, enzymatic bioreactor for enzyme replacement therapy, AAPS Annual Meeting, 7 (1995).
78. C. M. Chang and R. Bodmeier, Monoglyceride-based liquid crystalline injectable drug delivery systems, AAPS Annual Meeting, 228 (1995).
79. L. E. Appel, L. Rajewski, P. Leppert, and G. Zentner, In vivo evaluation of monoolein cubic phase gels in a mouse model, AAPS Annual Meeting, 299 (1996).
80. P. Lading, Y. Lundsholm, and T. Norling, Method and composition for controlled delivery of biologically active agents, International Patent WO 92/09272 (1992).
81. T. Norling, P. Lading, S. Engström, K. Larsson, N. Krog, and S. S. Nissen, Formulation of a drug delivery system based on a mixture of monoglycerides and triglycerides for use in the treatment of periodontal disease, J. Clin. Periodont., 19, 687–692 (1992).
82. P. B. Geraghty, D. Attwood, J. H. Collett, Y. Dandiker, and A. R. B. Smith, A monoolein lyotropic liquid crystalline system to deliver oxybutynin hydrochloride, AAPS Annual Meeting, 206 (1995).
83. P. B. Geraghty, D. Attwood, J. H. Collett, and Y. Dan-

diker, The in vitro release of some antimuscarinic drugs from monoolein/water lyotropic liquid crystalline gels, Pharm. Res., 13, 1265–1271 (1996).
84. K. Larsson, Cubosome and Hexosomes for drug delivery, Proc. Int. Symp. Controlled Release Bioact. Mater., 24, 198–199 (1997).
85. S. Engström, B. Ericsson, and T. Landh, A Cubosome formulation for intravenous administration of somatostanin, Proc. Int. Symp. Controlled Release Bioact. Mater., 23, 89–90 (1996).
86. B. Siekmann, H. Bunjes, M. H. J. Koch, T. Carlson, and K. Westesen, Synchrotron X-ray investigation of the structure of colloidal dispersions of liquid crystalline monoolein-water phases, Proc. Int. Symp. Controlled Release Bioact. Mater., 24, 943–944 (1997).
87. B. Ericsson, K. Larsson, and K. Fontell, A cubic protein-monoolein-water phase, Biochim. Biophys. Acta, 729, 23–27 (1983).
88. V. Razumas, A cubic-monoolein-cytochrome c-water phase: X-ray diffraction, FT-IR, differential scanning calorimetric, and electrochemical studies, J. Phys. Chem., 100, 11766–11774 (1996).
89. V. Razumas, Z. Talaikyte, J. Barauskas, K. Larsson, Y. Miezis, and T. Nylander, Effects of distearoylphosphatidylglycerol and lysozyme on the structure of the monoolein-water cubic phase: X-ray diffraction and Raman scattering studies, Chem. Phys. Lipids, 84, 123–138 (1996).
90. Y. D. Sadhale and J. Shah, Glyceryl monooleate (GMO)–water cubic phase gel as a physical stability enhancer of insulin, AAPS Annual Meeting, 234 (1995).
91. Y. D. Sadhale and J. Shah, The effect of water-mobility and viscosity on the physical stability of insulin in a glyceryl monooleate–water cubic phase gel, AAPS Annual Meeting, 92 (1996).
92. Y. D. Sadhale and J. Shah, Glyceryl monooleate (GMO)–water cubic phase gel as a stability enhancer of drugs, Pharm. Res., 12, S-234 (1995).
93. Y. D. Sadhale and J. Shah, Glyceryl monooleate (GMO)–water cubic phase gel as a stability enhancer of drugs, AAPS Annual Meeting, 234 (1995).
94. R. Wallin, S. Engström, and C. F. Mandenius, Stabilisation of glucose oxidase by entrapment in a cubic liquid crystalline phase, Biocatalysis, 8, 73–80 (1993).
95. J.-E. Löfroth, A. Andreasson, and G. Rehmberg, Liquid crystalline phases as delivery systems for drugs, Proc. Int. Symp. Controlled Release Bioact. Mater., 15, 380–381 (1988).
96. W. Buchheim and K. Larsson, Cubic lipid-protein-water phases, J. Colloid Interface Sci., 117, 582–583 (1987).
97. H. Okada, I. Yamazaki, Y. Ogawa, Sh. Hirai, T. Yashiki, and H. Mima, Vaginal absorption of a potent luteinizing hormone-releasing hormone analogue (Leuprolide) in rats. I: Absorption by various routes and absorption enhancement, J. Pharm. Sci., 71, 1367–1371 (1982).
98. Ch.-M. Chang and R. Bodmeier, Monoglyceride-based liquid crystalline topical drug delivery systems, Pharm. Res., 11, S-185 (1994).
99. K. Larsson and G. Lindblom, Molecular amphiphile bilayers forming a cubic phase in amphiphile-water systems, J. Dispersion Sci. Technol., 3, 61–66 (1982).
100. Y. Sadhale and J. C. Shah, Glyceryl monooleate cubic gel as chemical stability enhancer of cefazolin and cefuroxime, Pharm. Dev. Technol., 3, 549–556 (1998).
101. S. Engström, H. Ljusberg-Wahren, and A. Gustafsson, Bioadhesive properties of the monoolein-water system, Pharm. Technol. Eur., 14–17 (February 1995).
102. L. S. Nielsen, L. Schubert, and J. Hansen, Bioadhesive drug delivery systems. I. Characterisation of mucoadhesive properties of systems based on glyceryl mono-oleate and glyceryl monolinoleate, Eur. J. Pharm. Sci., 6, 231–239 (1998).
103. B. Sesta and A. D'Aprano, The transport of ions across monoolein bilayers mediated by synthetic macrocyclic carriers, J. Solution Chem., 18, 1163–1171 (1989).
104. C. Barth, H. Bihler, M. Wilhelm, and G. Stark, Application of a fast charge-pulse technique to study the effect of the dipolar substance 2,4-dichlorophenoxyacetic acid on the kinetics of valinomycin mediated K^+-transport across monoolein membranes, Biophys. Chem., 54, 127–136 (1995).
105. T. Petersson, S. Engström, and H. Nyqvist, Interaction of clomethiazole with model membranes, Proc. Int. Symp. Controlled Release Bioact. Mater., 23, 467–468 (1996).
106. T. Petersson-Nordén, A. Kansanen, H. Nyqvist, and S. Engström, A new method to determine the lipid bilayer/water partition coefficient by means of a cubic phase, Proc. Int. Symp. Controlled Release Bioact. Mater., 24, 553–554 (1997).
107. J. Engblom and S. Engström, Azone® and the formation of reversed mono- and bicontinuous lipid-water phases, Int. J. Pharm., 98, 173–179 (1993).
108. V. Razumas, J. Kanapieniené, T. Nylander, S. Engström, and K. Larsson, Electrochemical biosensors for glucose, lactate, urea, and creatinine based on enzymes entrapped in a cubic liquid crystalline phase, Anal. Chim. Acta, 289, 155–162 (1994).
109. G. Rummel, A. Hardmeyer, M. Loewen, J. P. Rosenbusch, and E. M. L. Biozentrum, Crystallization of bacteriorhodopsin in lipidic cubic phases, 7th International Conference on the Crystallisation of Biological Macromolecules, Granada, Spain, May 3–8, 1998.