CHAPTER II

LITERATURE REVIEW

1. Definition of Liquid Crystals (Brown, 1972; Vyas et al., 1997)

The liquid crystalline state, also called mesophase or mesomorph, is the intermediate state of matter between crystalline solid and isotropic liquid. At the molecular level, two extreme cases can be recognized: the perfect order of crystals in which molecules exhibit no mobility at all and the complete disorder of gases and liquids which exhibits randomness of highly mobile molecules. When both of the principles of order and mobility are applied in combination, a new state of matter originates and is named the liquid crystalline state. This state of matter combines the order of a crystal with the mobility of an isotropic liquid and, thus, possesses some specific characteristics. One of the most important properties of liquid crystals is being birefringent, a property which is associated with crystals. On the other hand, they have the flow properties of liquids. These properties have rendered liquid crystals a wide range of applications in the pharmaceutical field. For example, liquid crystals are so important in emulsions that they have been included in the International Union of Pure and Applied Chemistry (IUPAC) definition of an emulsion where an emulsion is defined as a mixture of two immiscible liquids, one of which is dispersed in the other in the form of liquid droplets and or as liquid crystals.

2. Classification of Liquid Crystals

Liquid crystals can be grouped into two major classes depending upon the mechanism of their formation (Brown, 1972; Lawrence, 1994; Vyas, et al., 1997).

2.1 Thermotropic Liquid Crystals

Thermotropic liquid crystals are prepared by heating the crystalline solid. Temperature is the primary factor in achieving this system. There are three different types of thermotropic liquid crystals: smectic, nematic, and cholesteric (Figure 1). In the smectic phase, molecules are arranged in the form of layers, and the axis of the molecule is nearly normal to the plane of the layers. In the nematic phase, the molecules maintain parallel arrangement along their long axes but are not stratified. In the cholesteric phase, the molecular axes are parallel to the plane of the layers, but the direction of the long axes of the molecules changes continuously in going from one layer to another, resulting in a helical structure. Thus, thermotropic liquid crystalline systems can be defined as nematic, smectic or cholesteric depending on the orientation and the repetition properties of the units. These liquid crystals are commonly found in our daily life and show multiple applications as they exhibit variations in color with temperature and/or a magnetic field and/or an electric field. Materials that can form thermotropic liquid crystals include cholesteryl palmitate and p-azoxyanisole. Some applications of thermotropic liquid crystals include thermometers and liquid crystal displays (LCD).

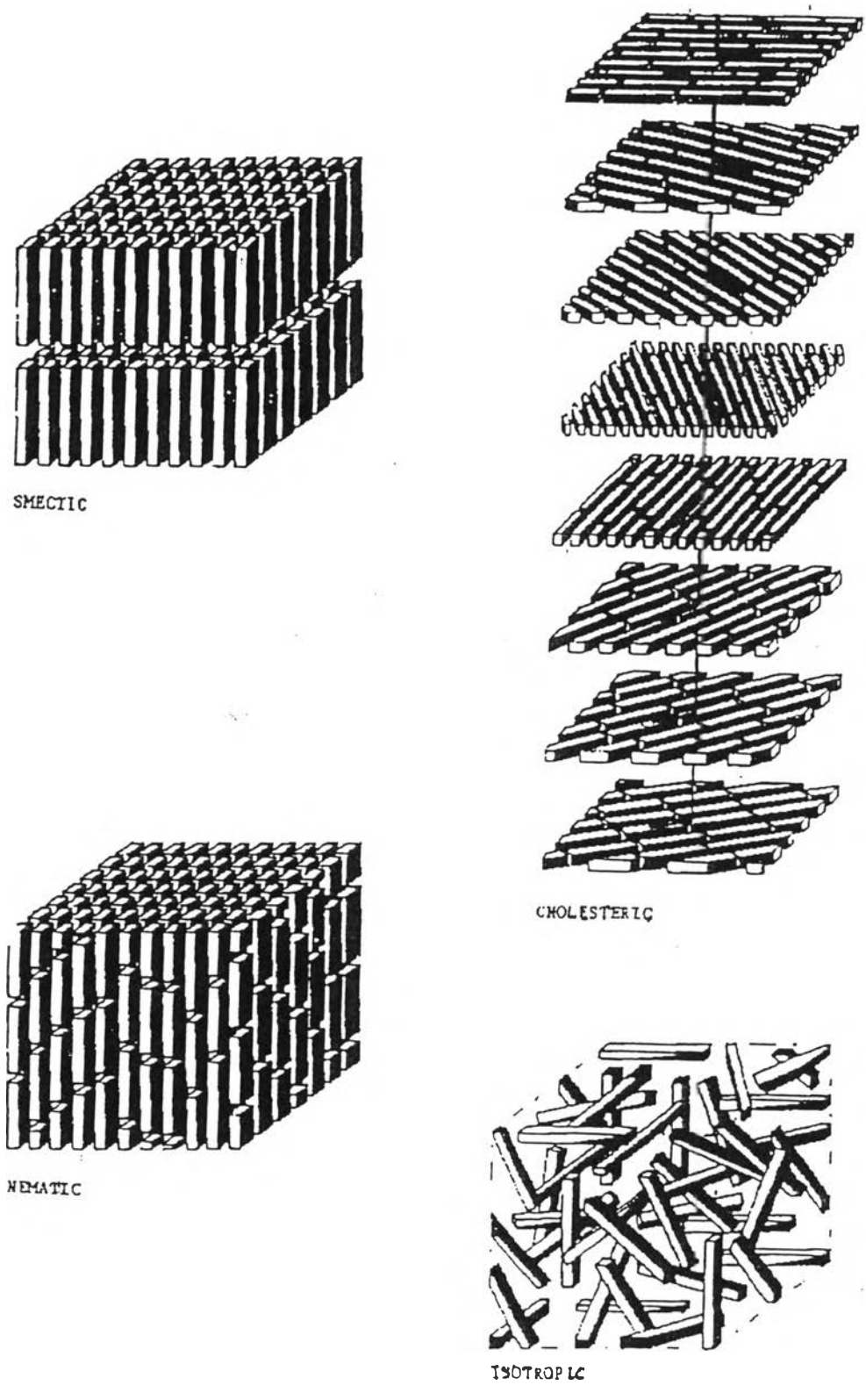


Figure 1. Thermotropic Liquid Crystals. (From Reprinted ICI Surfactants Document RP94/93E)

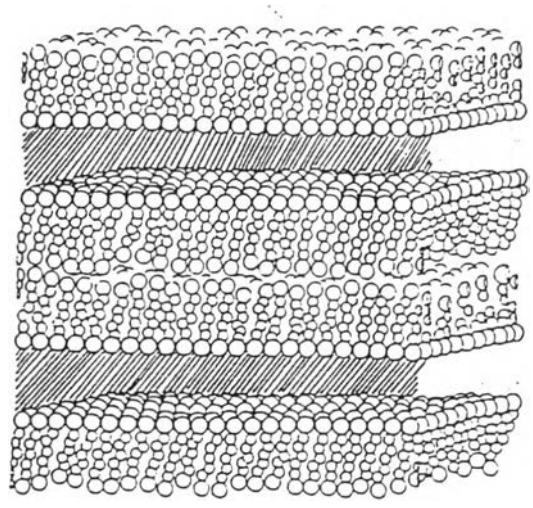
2.2 Lyotropic Liquid Crystals

Lyotropic liquid crystals are prepared by mixing two or more components, one of which consists of polar molecules (e.g., water). The other component(s) may be an organic or an inorganic compound. Temperature change is not the factor in achieving a lyotropic liquid crystalline system, but rather the change in solvent content.

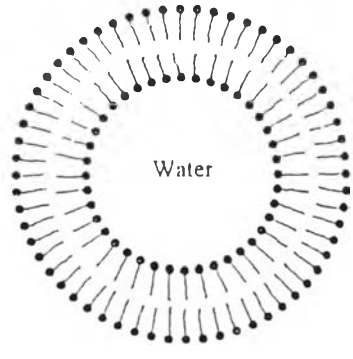
Many amphiphilic compounds which contain both hydrophobic and hydrophilic parts, such as surfactants and lipids, have a tendency to form lyotropic liquid crystals. These amphiphiles can incorporate considerable amounts of water leading to the formation of various liquid crystalline phases. Several studies reported the phase behavior of amphiphilic compounds both in an aqueous environment (Lutton, 1965; Kayali et al., 1991) and in a nonaqueous environment (Friberg and Liang, 1987) where lyotropic liquid crystalline phases exist. Not only surfactants, but other components in the system, such as oils and long chain alcohols, also participate in building up the structures (Rong and Friberg, 1988; Mueller-Goymann and Frank. 1986). When a surfactant is dispersed in water just above the limit of its aqueous solubility (i.e., above its critical micelle concentration), it generally aggregates into one of the three types of structure, namely lamellar, hexagonal, and cubic phases, depending upon many factors.

a) <u>The Lamellar Phase (Eccleston, 1990)</u>

In the lamellar phase, molecules are arranged in bilayers separated by water layers which are extended into planar bilayers or closed bilayer systems (vesicles or liposomes) (Figure 2). At normal surfactant concentrations, the volume proportion of the lamellar phase can become so large in an emulsion system that it not



(a)



(b)

Figure 2. Lamellar Phases: (a) Planar Bilayer (b) Closed Bilayer [Vesicle or Liposome]. (From Kayali, 1991; Rieger, 1997)

only covers the droplets as a stabilizing film but also forms a macroscopic phase in which the droplets are dispersed (Figure 3). In such system, contact between the polar-polar and the nonpolar-nonpolar portions of the molecules is maximized, resulting in a stable configuration. The hydrocarbon chains of the bilayer can exist in two different states: the gel state and the liquid crystalline state (Figure 4). The structure of the lamellar gel state resembles that of the lamellar liquid crystalline state, but in the

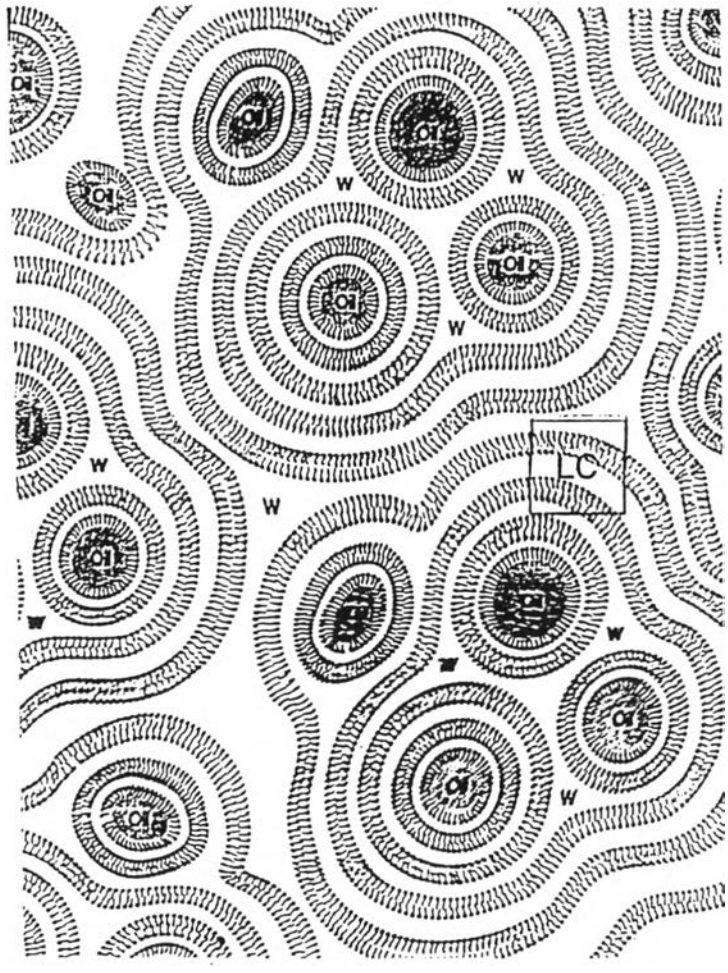
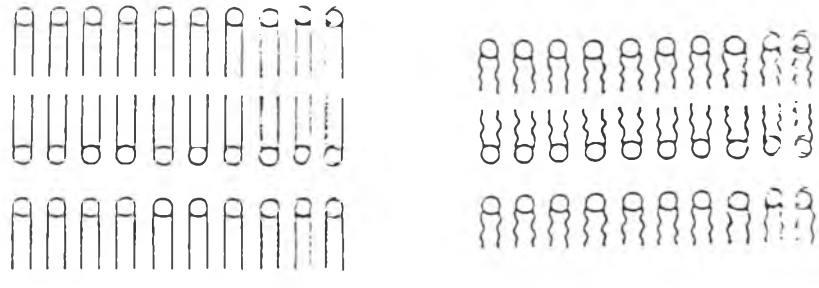


Figure 3. Structure of an Oil/Liquid Crystal/Water Emulsion. (From Forster, 1997)



(a) **(b)**

Figure 4. States of the Hydrocarbon Chains of the Bilayer Structure: (a) Gel State; (b) Liquid Crystalline State. (From Maulik Shipley, 1996)

gel state the molecules pack more tightly (smaller surface area per molecule), and the chains are much more highly ordered and essentially fully extended. In the liquid crystalline state, there is considerable disorder in the acyl chain. Because the chains are maximally extended in the gel phase with the molecules packing more tightly together, the bilayer thickness is more than that of liquid crystalline phase, and the density of gel phase is slightly greater. During a gel to liquid crystalline transition, the polar head, as well as the lipid hydrocarbon tail, becomes less dense.

Temperature can also markedly influence the physical state of the system. The acyl chain of the bilayer can exist either in liquid crystalline state or in gel state, depending on the transition temperature (T_m). T_m is the melting temperature of the hydrocarbon chain without any loss of long range stacked bilayer structure. T_m is influenced primarily by the characteristics of the hydrophobic portion of the surfactant. The lamellar liquid crystalline phase exists above the phase transition temperature of the system, whereas bilayer gel phase exists below this temperature. The lamellar liquid crystalline phases that occur above the phase transition temperature have been called the L_α phase. Bilayer gel phases that occur below the phase transition temperature are referred to as the L_β phase.

b) <u>The Hexagonal Phase</u>

In this phase, the molecules are arranged in the form of cylinders either with the polar groups on the outside and in contact with water (normal hexagonal/ H_I) or with the polar groups facing the inside where there is a column of water (reverse hexagonal/ H_{II}). These cylinders are packed in a hexagonal array in a continuous

aqueous medium (Figure 5). The hexagonal phase is much stiffer in consistency than the lamellar phase.

c) The Cubic Phase

The cubic phase represents another form of a liquid crystalline phase. It consists of molecules packing in a spherical pattern. The spheres of molecules then arrange themselves in a cubic pattern, as is schematized in Figure 6. Cubic phases form structures with long-range three-dimentional periodicity, where the molecules still exhibit a dynamic disorder. The network structure makes the phase very viscous, and the cubic phase is sometimes referred to as the 'viscous isotropic phase' in the literature (Engstrom, 1992). A number of reviews of the cubic phase in general have been published, discussing various aspects such as its structure and biological relevance (Lindblom et al., 1979; Lindblom and Rilfors, 1989; Larson.1989).

The most interesting aspect of these liquid crystals is their ability to incorporate both lipophilic and hydrophilic agents into the corresponding lipophilic and hydrophilic regions of their structures. The compounds reported to be efficiently incorporated into liquid crystalline systems include drugs, vitamins, and sunscreen agents (Wahlgren et al., 1984; Rong et al., 1995; Uslu, Yuksel, and Baykara, 1997).

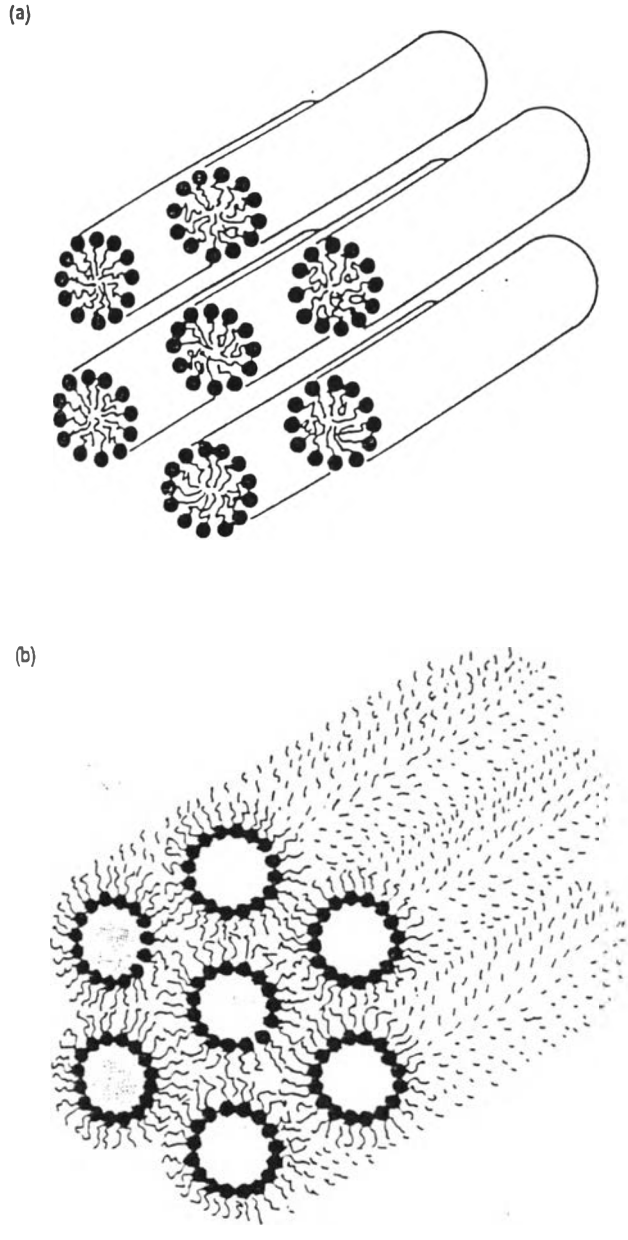


Figure 5. The Normal and Reverse Hexagonal Phases: (a) H_I; (b) H_{II}. (From Seddon and Cevc, 1993)

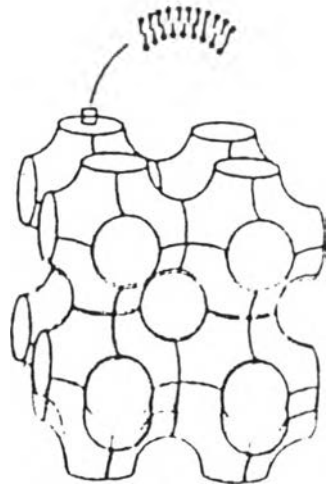


Figure 6. Cubic Phase. (From Engstrom et al., 1992)

3. Structure Determination of Liquid Crystalline Phase (Rosevear, 1954; Friberg, 1979; Gennis, 1989)

The formation of various mesophases upon hydration can be determined by various methods, but the three commonly used techniques are polarized light microscopy, differential scanning calorimetry, and small angle X-ray diffraction.

3.1 *Polarized Light Microscopy*

Among all the available techniques, polarized light microscopy provides the easiest way to qualitatively idenify the different phases of liquid crystals by their

textures. The lamellar and the hexagonal phases are optically anisotropic, and thus can be directly observed under an optical microscope with polarized light. The sample of these phases will look radiant when viewed against a light source placed between crossed polarizers, whereas the cubic phase is optically isotropic and consequently not visible in polarized light. Therefore, the characterization of cubic phase requires other techniques. Under the microscope with polarized light, the two phases, the lamellar and the hexagonal, also display different patterns (Rosevear, 1954) (Figure 7 and Figure 8). These patterns are very useful for primary identification. This technique was used by several researchers who previously studied liquid crystals (Wahlgren et al., 1984; Ibrahim et al., 1992; Chang and Bodmeier, 1997).

3.2 Differential Scanning Calorimetry (DSC)

The hydrocarbon chains of amphiphilic molecules are subjected to undergoing a transformation from an order (gel) state to a more disorder (liquid crystalline) state. These changes have been characterized by differential scanning calorimetry. The parameters usually gained from this technique are the following:

-Transition temperature, T_m : the temperature at the maximun peak height for which the transition occurs

-Transition enthalpy, ΔH: the actual heat required for the entire transition normalized per mole or per unit weight or the entire area under the curve of the transition peak (Gennis, 1989)

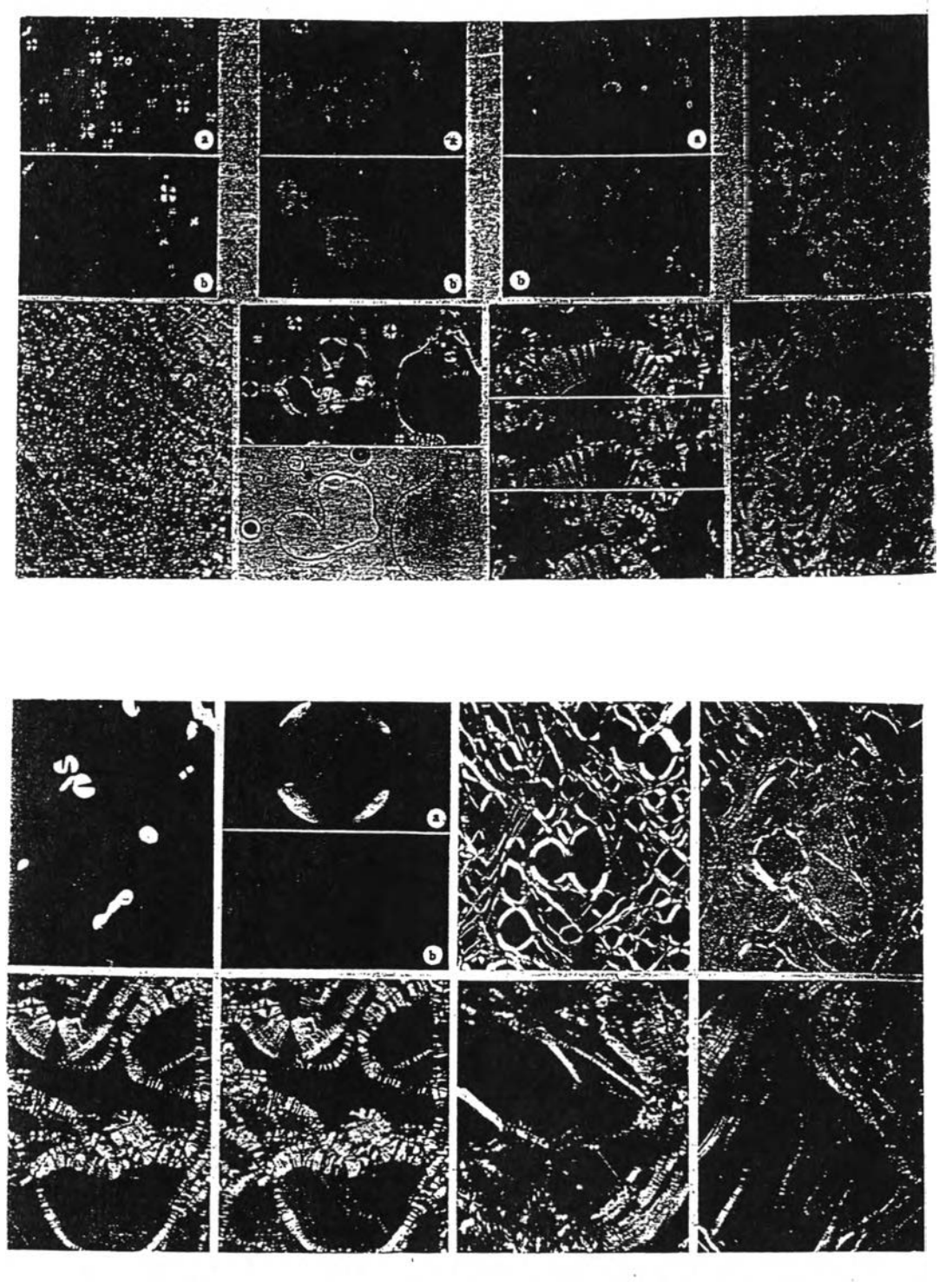


Figure 7. Textures of Lamellar Phase Under the Polarized Light Microscope.

(From Rosevear, 1954)

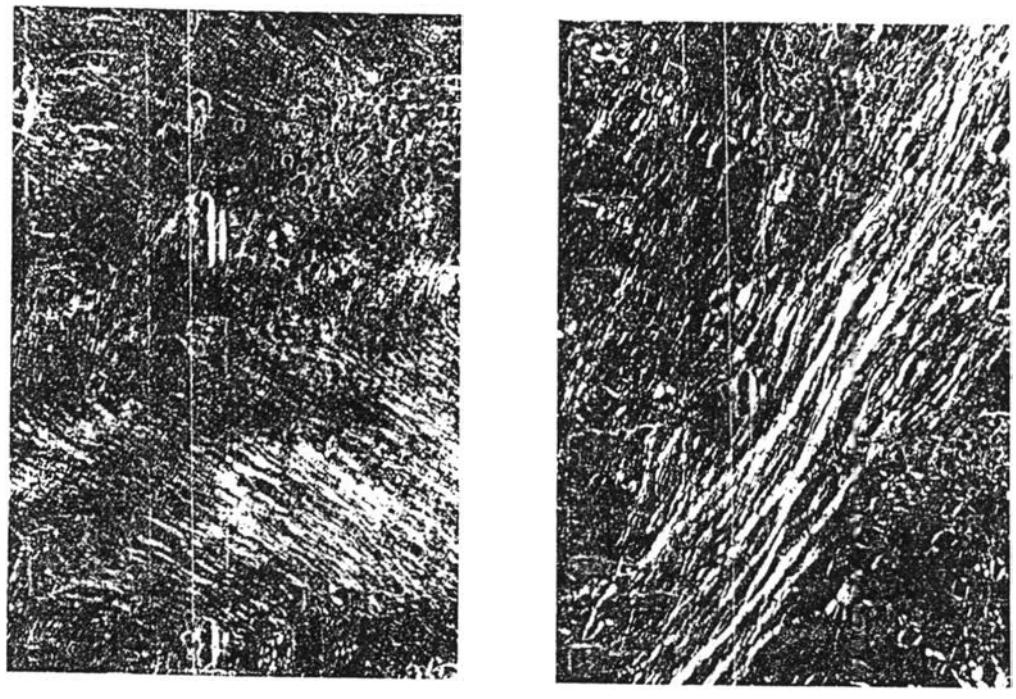


Figure 7. (continued) Textures of Lamellar Phase Under the Polarized Light Microscope. (From Suhaimi, Ahmad, and Friberg, 1993)

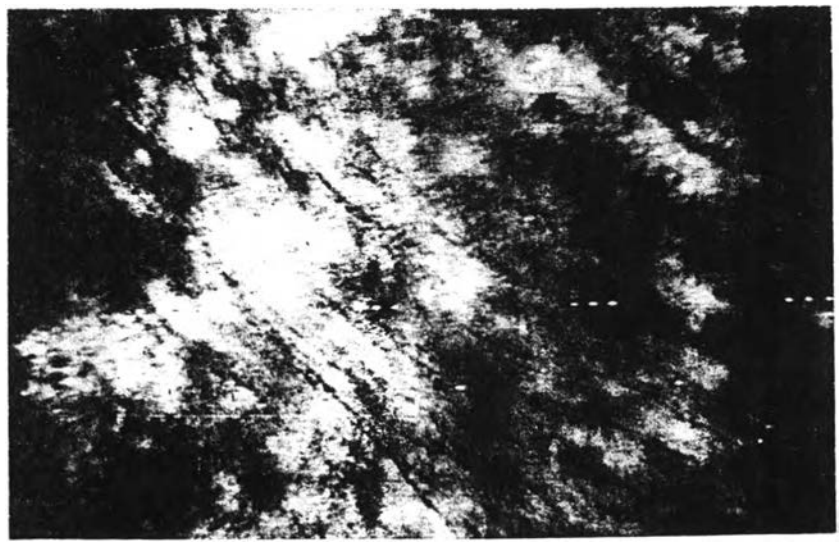


Figure 8. Textures of Hexagonal Phase Under the Polarized Light Microscope. (From Ibrahim, Sallam, and Habboub, 1992)

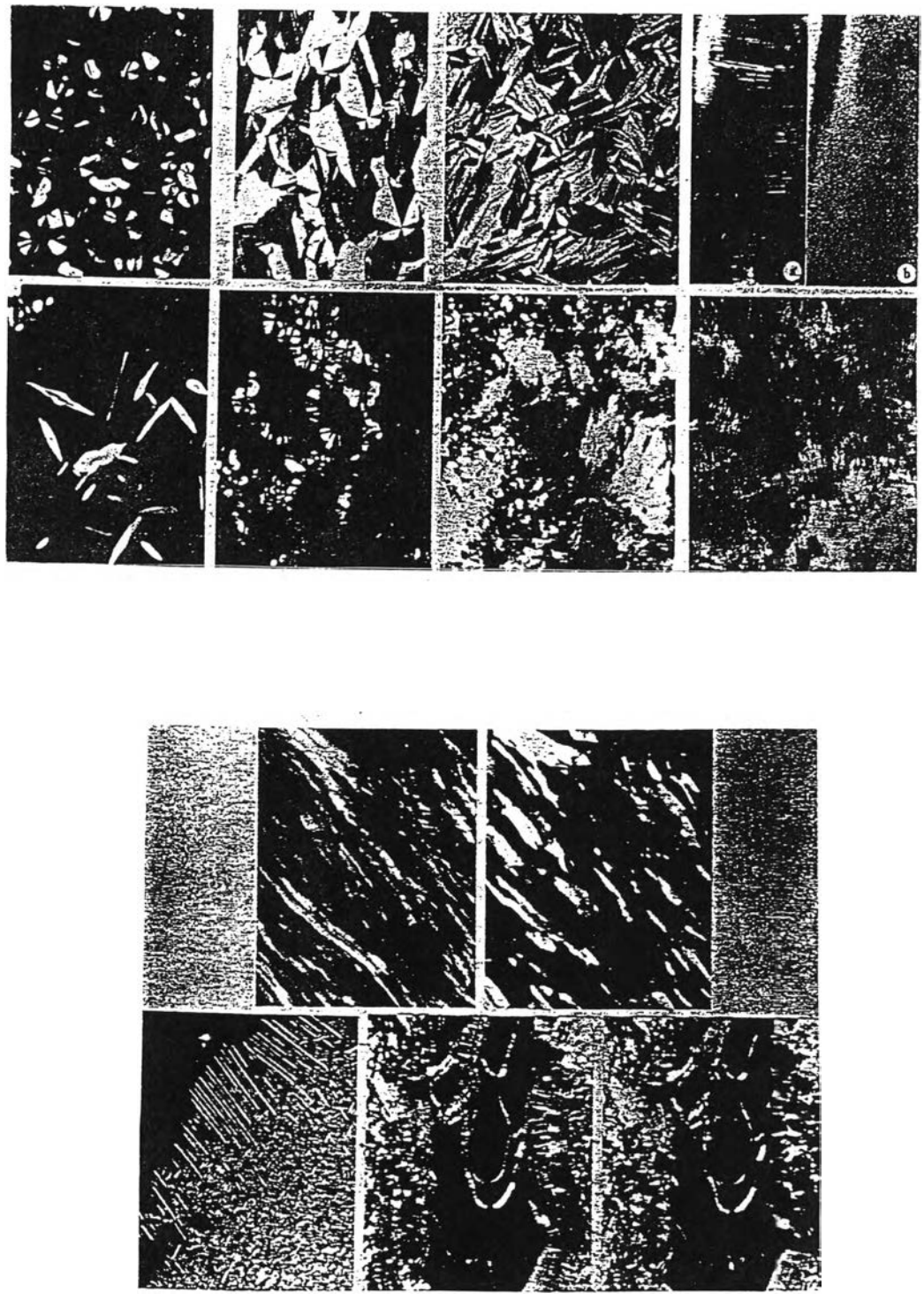


Figure 8. (continued) Textures of Hexagonal Phase Under the Polarized Light Microscope. (From Rosevear, 1954)

Figure 9 illustrates a thermogram displaying the gel to liquid crystalline transition with relevant thermodynamic parameters.

3.3 Small Angle X-Ray Diffraction

Small angle X-ray diffraction technique has been particularly valuable in determining the type of liquid crystal phase (Friberg, 1979). The ratio between the characteristic distances from the film are different among the phases. The ratio is 1:1/2:1/4 in the lamellar phase, $1:(1/3)^{1/2}:(1/4)^{1/2}$ in the hexagonal phase, and $1:1/(3/4)^{1/2}:1/(3/8)^{1/2}$ in the cubic phase. The interlayer spacings of the liquid crystalline phases (Figure 10) can be estimated by small angle X-ray diffraction method (Suhaimi, Ahmad, and Friberg, 1995). The interlayer spacing was determined by the standard Bragg's equation:

$$n\lambda = 2d\sin\theta$$

where n is the order of diffraction, λ is the wavelength of the incident X-ray beam, d is the interlayer spacing, and 2θ is the diffraction angle. The diffraction angle is calculated by

$$\tan(2\theta) = DS / 2(l + X)$$

where D is the distance between the peaks obtained from the X-ray measurements, S is a calibration factor associated with the detector, l is the length (in mm) between the sample and the detector, and X is the calculated length (in mm) from the calibration curves.

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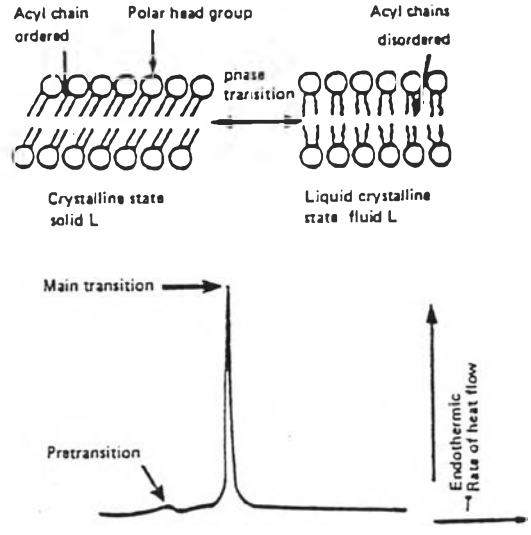

Figure 9. Phospholipid Gel to Liquid Crystalline Phase Transition. (From Weiner, Martin, and Riaz, 1989)

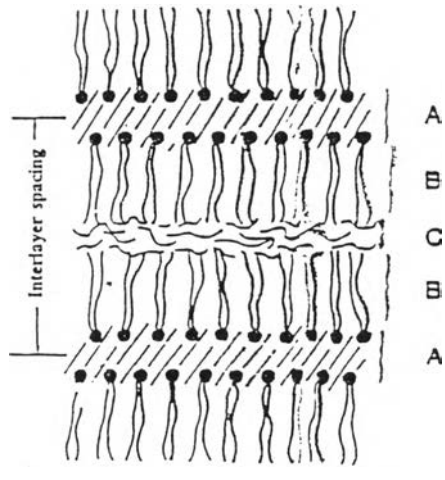

Figure 10. The Lamellar Liquid Crystal is Divided into Three Zones: (A) Water Layer, (B) Amphiphiles, (C) Space Between the Terminal Methyl Groups. (From Friberg et al., 1993)

The bilayer thickness d_0 and the water layer thickness d_W is given by

$$d_0 = (1\text{-}c)v_1 d / (1\text{-}c)v_1 + cv_W$$

$$d_W = d - d_0$$

where c is the weight fraction of water, and v_1 and v_W are the partial specific volume of amphiphilic molecule and water, respectively. Since v_1 is difficult to estimate, some authors used $v_1 = v_W = 1$ ml/g as an approximation.

Polarizing microscopy is a useful and rapid way to characterize the structure of liquid crystals. It can be used as a routine technique. In order to obtain an understanding of what is occurring at the structural level, however, DSC and X-ray diffraction studies of the system are usually employed. Researchers uesd these techniques to investigate molecular arrangements of liquid crystalline structures both before and after the incorporation of many solutes to study the possible interaction of these solutes with the liquid crystalline structures. Tenchove et al. (1996) studied the effect of sucrose on the properties of phosphatidylethanolamine bilayers by DSC and X-ray diffraction. They reported that sucrose increases the transition temperature and decreases the interlamellar spacing of the phospholipid bilayer. Other examples that used DSC and X-ray diffraction to study the interaction of solutes with liquid crystalline structure include the study of the effect of sucrose on the properties of phosphatidylcholine bilayer, the interaction of lidocaine and lidocaine-HCl with the liquid crystal structure, and the results from the addition of curcumin into the bilayer structure. (Stumpel et al., 1985; Mueller-Goymann and Frank, 1986; Suhaimi et al., 1995).

4. Lyotropic Phase Transition

Lyotropic phase transition between the lamellar gel and liquid crystalline phases, or between the lamellar and the inverted hexagonal phases, as well as between other mesomorphic forms, depends on several factors which include the following:

4.1 The presence of additional substances

4.2 The ratio of surfactant and water

4.3 The temperature of the system

4.4 The structural properties of the amphiphilic molecules (molecular geometry)

The Presence of Additional Substance

The presence of a solute dissolved in the mesophase can influence the structure of the liquid crystal and cause a change in its formation. Ibrahim et al. (1993) investigated the effects of increased concentration of the solutes; salicylic acid, benzoic acid, and o-, m-, and p-methoxybenzoic acids; on the properties of lamellar liquid crystals composed of 37% polyoxyethylene(20)isohexadecyl ether in aqueous buffer. They found that a phase change occurred in the liquid crystal from a lamellar to a hexagonal structure in the case of salicylic acid, benzoic acid, and m-methoxybenzoic acid when the solute concentration reached a certain level. However, o- and p-

methoxybenzoic acids showed no effect on the structure of the liquid crystal in the concentration range studied. Kriwet and Mueller-Goymann (1995) found that the addition of more than 4.5% of diclofenac diethylamine to phospholipid-water system led to phase transition from liquid crystals to microemulsions, and the release of the drug was altered. In general, the structure of liquid crystal is influenced by the characteristic of the solute as well as the solute content, and it is also influenced by the form of the solute added. Engstrom (1992) found that the cubic phase formed in the monoolein-water system was transformed into a lamellar liquid crystalline phase on the addition of lidocaine HCl and to a reverse hexagonal liquid crystalline phase or a reversed micellar phase when the base form of the drug was added. Therefore the interaction between the functional groups of the solute molecules and those of molecules constituting the mesophase can affect molecular packing of liquid crystalline systems.

Solutes such as ions can interact directly with the headgroup of structure-forming components of the liquid crystalline system. This may lower the affinity of the headgroup for water or may neutralize charges, giving rise to intermolecular forces and resulting in tighter molecular packing. Such solutes, therefore, typically increase the phase transition temperature (Powell et al., 1994). As mentioned earlier, uncharged water-soluble solutes, such as sucrose, also affect the stucture of liquid crystal probably by imposing a dehydration effect on the head group of the bilayer-forming components, resulting in a system with more tightly-packed molecular structure and thus increasing the phase transition of the system.

The Ratio of Surfactant and Water

The ratio of surfactant and water is another factor affecting lyotropic phase transition. Geraghty et al. (1996) found that glyceryl monooleate, a water-insoluble monoolein which swells in water and forms various types of lyotropic liquid crystalline structures, at ambient temperature with initial contents of less than 15% w/w of water formed a lamellar phase structure consisting of planar lipid bilayers with alternating water layers. When the water content increased, the system entered the cubic phase structure region.

The Temperature of the System

Phase transition can occur as a result of changes in temperature. Geraghty et al. (1996) found that at ambient temperature, gel from monoolein formed lamellar and cubic phase structures, whereas at temperature greater than 57^0C, they formed a reverse hexagonal (H_{II}) phase structure.

The Structural Properties of the Amphiphilic Molecules (Molecular Geometry) **(Myers, 1997)**

As mentioned above, amphiphilic molecules can form various structures depending upon many factors. Those structures can change rapidly as conditions are

altered. Prediction of the structure of surfactant aggregates can be done by analysis of geometric characteristics of the molecule defined as a critical packing parameter:

$$P_c = v/a_0 l_c$$

where P_c is the critical packing parameter,

a_0 is the minimum interfacial area occupied by the surfactant head groups,

v is the volume of the hydrophobic tails, and

l_c is the maximum extended chain length of the tail in a "fluid" environment such as the core of the micelle, etc.

Using those three molecular parameters, the geometric approach allows one to predict the shape and size of aggregates. A summary of the predicted aggregation charateristics of surfactants covering the whole range of geometric possibilities is given in Table 1.

However, it has been found experimentally that the form of aggregate structure produced by a given surfactant depends to a great extent on its environment. Geometric considerations explain fundamental processes operating in the aggregation process based on the various effects the solution has on a_0, v, and l_c. Insertion of the appropritate values for sodium dodecyl sulfate (SDS) into the equation predicts the formation of spherical micelles, in agreement with experimental observations. The external conditions may also participate in determining the critical packing parameter and should be taken into consideration. For example in the case of SDS, the solvent conditions that alter one or more of the critical values (e.g., high salt concentration that

Table 1 Expected Aggregate Characteristics in Relation to Surfactant Critical Packing Parameter, P_c (From Myers, 1997)

P_c	Surfactant type	Expected structure
< 0.33	Simple, single chains and relatively large head groups	Spherical or ellipsoidal micelles
0.33-0.5	Simple, relatively small head groups, ionics in electrolyte	Relatively large cylindrical or rod-shaped micelles
0.5-1.0	Double-chain, large head groups and flexible chains	Vesicles and flexible bilayer structures
1.0	Double-chain, small head groups or rigid, immobile chains	Planar extended bilayers
> 1.0	Double-chain, small head groups very large, bulky hydrophobic groups	Reverse or inverted micelles

reduce the effective value of a_0) would, according to the equation, lead to cylindrical or disk-shaped micelles, again in agreement with experimental observations. Hence, the phase transition can occur when structural properties of amphiphiles change from the influence of external factors.

As described above, the structure of lyotropic liquid crystalline phases is dependent on several factors, and this can also play important roles regarding drug administration into human body. Schneeweis and Mueller-Goymann (1997) found that reverse micelles of diclofenac sodium encapsulated in soft gelatin capsules, upon contact with aqueous media, exhibited an induced transformation into a semisolid system of liquid crystal which slowed down drug release and might have some beneficial effects after rectal application. The other example was reported by Engstrom et al. (1992). They suggested that polar insoluble but swelling lipid such as monoolein formed a highly ordered cubic phase in excess of water, which can be used to sustain the release of different types of drugs. One problem with the cubic phase, however, is its stiffness which makes it difficult to handle. In order to make the administration of the cubic phase easier, precursor in the form of a lamellar phase was investigated. They found that the monoolein formed the lamellar phase at room temperature, and was converted to the cubic phase at human body temperature. This result may give a possibility of using the system for injectable drug delivery although its stiffness makes it difficult to pass through the needle.

Figure 11 illustrates the different liquid crystalline phases which are obtained when glycerl monooleate is dissolved in water. The influence of the concentration and the temperature on the physical structure of the system is demonstrated.

The influence of the molecular composition is also shown in the phase diagrams of various monoglycerol esters (Figure 12).

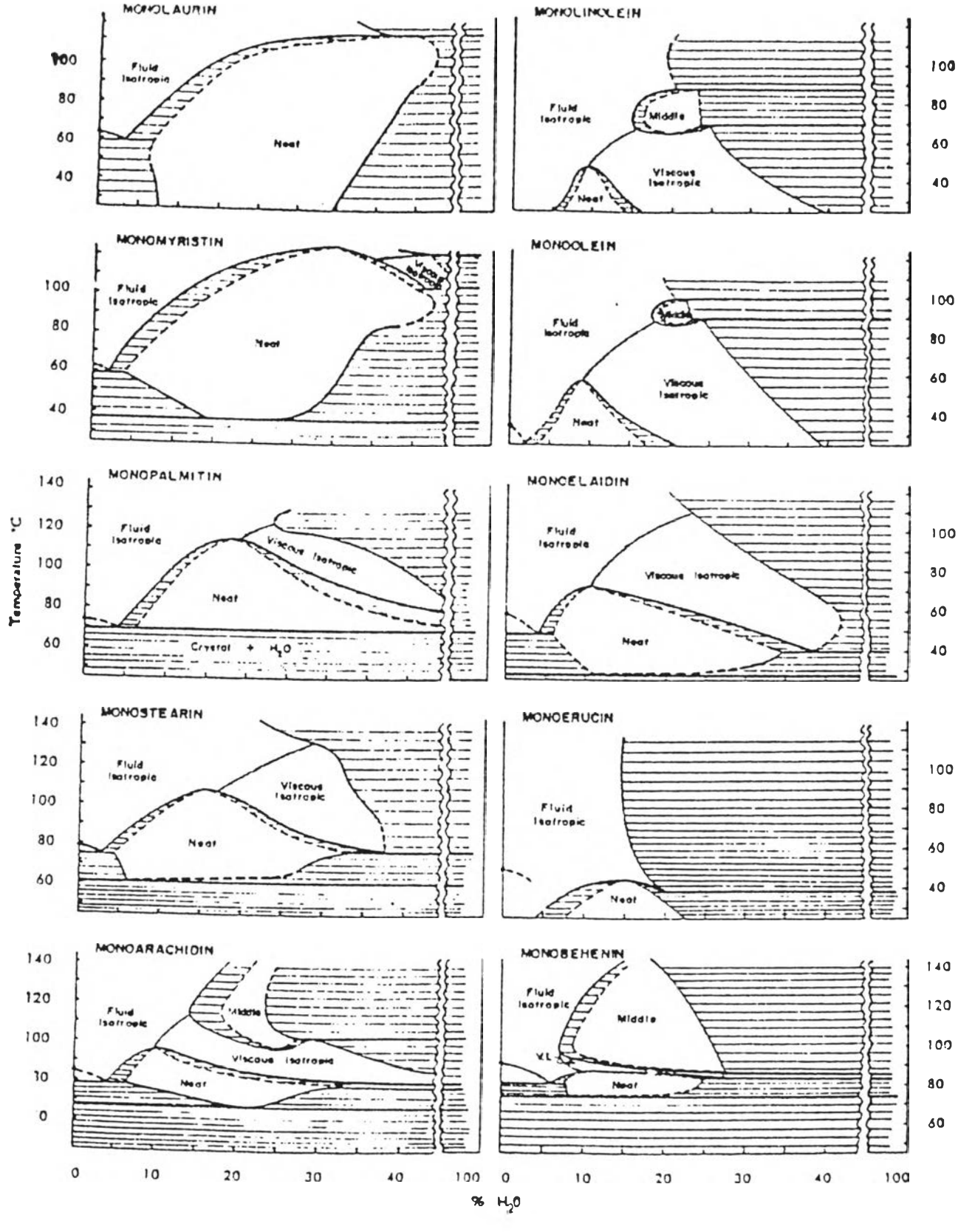

Figure11. Binary Phase Digram of Glyceryl Monooleate and Water. (From Geraghty et al., 1996)

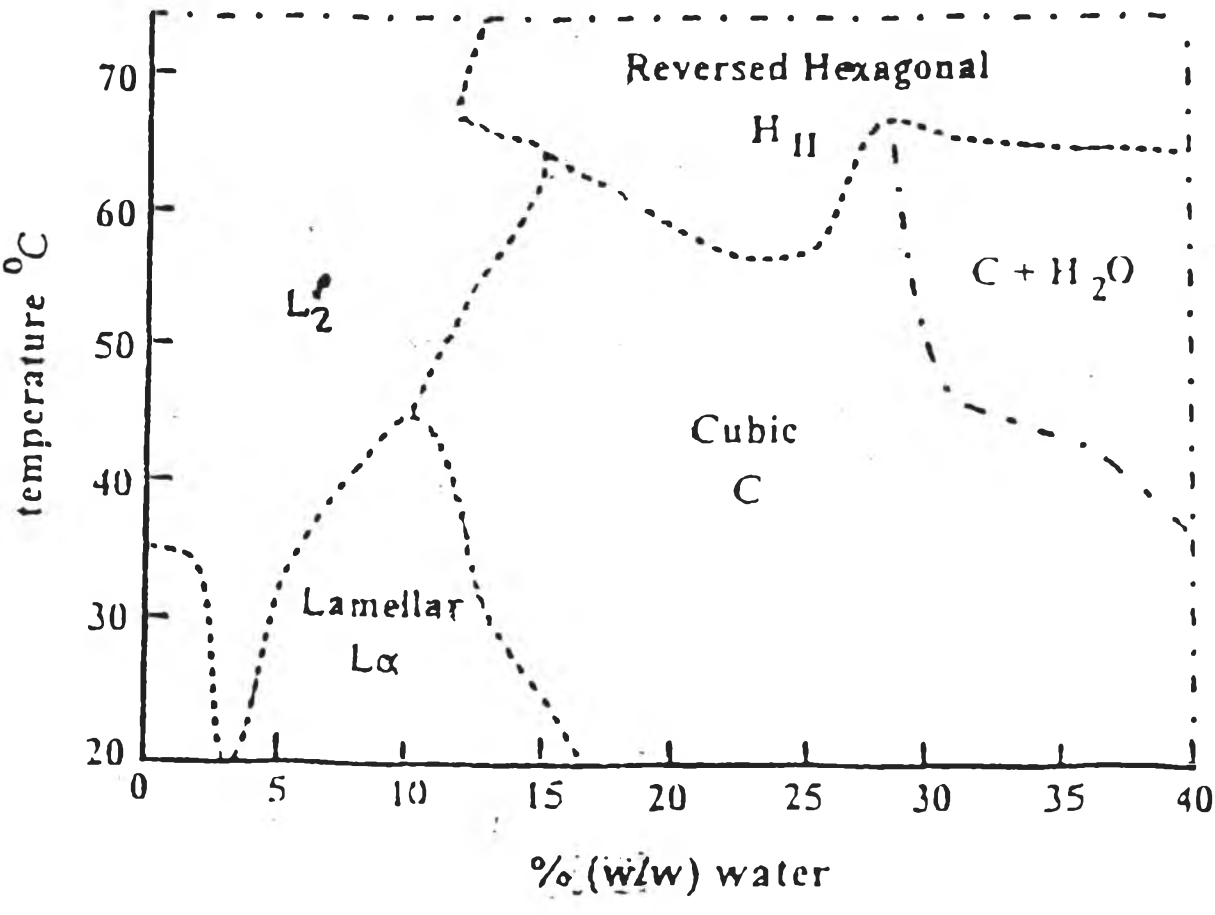

Figure 12. Binary Phase Diagram of Pure 1-Monoglycerides in Water. (From Lutton, 1965)

5. Advantages of Liquid Crystals

Liquid crystalline phase structures are currently recognized as important in pharmaceutical formulations. Such mesophases provide physical advantages to emulsion systems as well as therapeutic benefits.

5.1 Enhancement of Emulsion Stability

Compared to an emulsion of two liquids which is stabilized by a monolayer of the emulsifier, liquid crystals in an emulsion stabilize the system with several different mechanisms. The layer of liquid crystalline phase around the droplets acts as a rheological barrier to coalescence, slowing down the movement of the droplets. In addition, some liquid crystalline phases have a tendency to form a network extending through the continuous phase. This network also slows down the movement of droplets and enhances the stability of the emulsion. The pronounced increase in stability of emulsions when the liquid crystalline phase is present has been evident (Friberg and Mandell, 1970; Tyls and Frank, 1990).

5.2 Control of Drug Delivery

In a normal emulsion of liquids, the diffusion across the interface is little hindered, and the release of substance from the droplets to the continuous phase is fast. The liquid crystalline phase is shown to sustain the release of drugs. The structure of the liquid crystal effectively reduces the transport of a dissolved substance. In liquid crystalline systems, the release is lower than in those without stabilization by the liquid

crystalline phase. Geraghty et al. (1996) found that the in vitro release of some antimuscarinic drugs from monoolein/water liquid crystalline system was sustained over a period of about 18 hours. Other examples are controlled release of lidocaine and lidocaine-HCl from surfactant bilayers in a system consisting of soyasterol-PEG-ether, water and the drugs; fenoprofen from phospholipid bilayers; and chlorpheniramine maleate and pseudoephedrine hydrochloride from monoolein/water cubic phase (Mueller-Goymann and Frank,1986; Mueller-Goymann and Hamann,1993; Geraghty et al.,1996; Chang and Bodmeier, 1997).

5.3 Prolongation of Hydration Properties of dosage forms

The water in the structure of liquid crystalline phase is less prone to immediate evaporation when applied to surface such as the skin. So, when applied topically, such phases increase the length of time the skin can retain moisture compared to emulsions having no such phases and thus increase hydration of the skin. Friberg and Kayali (1989) showed that water evaporation rates from liquid crystals were significantly slower than those measured from unprotected water surface. Hydration level of the skin is one of the factors that affect skin permeability characteristics, for example, hydrated skin demonstrated higher permeability for a series of salicylate esters (Feldmann and Maibach, cited in Bary, 1993).

5.4 Solubilization of Low Solubility Drugs

The liquid crystal can solubilize higher amounts of some substances than can normal liquids, depending on the structure of the substance as well as the type

of liquid crystalline phase. A good example is the study with hydrocortisone by Wahlgren et al. (1984) where the drug was soluble in the lamellar liquid crystalline phase up to 5% by weight. This value is about four times greater than the corresponding solubility of hydrocortisone in the commonly used solvent, ethylene glycol.

5.5 Enhancement of Drug Stability

Systematic studies of reaction kinetics utilizing liquid crystalline structures as solvent media are scarce. Swarbrick and Carless (1964) studied the rate of oxidation of benzaldehyde in lyotropic mesophases encountered in ternary systems consisting of betaine-benzaldehyde-water. The reaction rates were found to be significantly lower in the mesophases when compared with the corresponding rates in isotropic systems. Murthy and Rippie (1970) studied the rate of hydrolysis of procaine and its quarternary derivatives in lyotrpic liquid crystalline phases. They found that the reaction rates were considerably slower (300 to 1100 folds) in the liquid crystalline phases than in aqueous media.

5.6 Similarity to Biological Membranes

There are many drugs the action of which is to affect the biological membrane such as antibiotics and disinfectants. Many of these drugs insert their actions by disrupting integrity of bacterial membranes. One example is farnesol. Addition of farnesol to the cell culture derived from human leukemia line CEM-C1 results in cell

shrinkage and cell death, indicating a possible effect on the cell membrane. It has become of interest to determine whether drugs could have a direct effect on membranes. Available literature (Kayali et al.,1991) indicates that the stratum corneum lipids are organized into a lamellar structure identical to the lamellar liquid crystals. The use of lamellar liquid crystals as the model membrane may help elucidate the mechanism of action of the drugs. This has been demonstrated by several groups of researchers including Pache et al. (1972). They reported that chlorotricin, an antibiotic, decreased the endothermic transition of dipalmitoylphosphatidylcholine (DPPC) phospholipid bilayers at 42 ^{0}C and removed it at 1:1 and 2:1 lipid drug ratio, respectively. Electron Spin Resonance (ESR), Nuclear Magnetic Resonance (NMR) and Optical Rotary Dispersion (ORD) showed that electrostatic interaction took place between the amino-groups of the antibiotic and the phosphate groups of the DPPC and the tails of chlorotricin penetrated into the lipid bilayer. Several studies have reported the use of liquid crystals as the model membrane (Ikeda et al, 1984; Berleur et al., 1984; Berleur et al., 1985; Aranda et al.,1988).

5.7 Applicability to Cosmetic Uses

Oily cosmetics such as waterproof foundations, eyeshadows, and lipsticks are usually difficult to be remove by cleansing creams or cleansing oils and tend to remain on the skin. Occasionally they are wiped off with a piece of tissue; however, this method may result in skin damage by skin scrubbing. Suzuki et al. (1992) found that by using a liquid crystalline system consisting of polyoxyethylene

(20) octyldodecyl ether as a make-up remover, oily cosmetics were easily dissolved and dispersed. Furthermore, this system could be easily removed from the skin by rinsing off. Another example is the work by Rong et al (1995) who used a liquid crystalline system to solubilize active agents for cosmetic purposes. Vitamin E, which is an anti-oxidant itself, is an oil, and its direct application is far from a satisfying cosmetic point of view because of its tackiness and oily appearance. They found that a liquid crystalline vehicle could solubilize vitamin E to an extent higher than the values obtained in traditional emulsion systems.

6. Potential Use of Liquid Crystals In Drug Delivery

Liquid crystalline phases have high potential in drug delivery. It is known that the release pattern of the entrapped drug molecules in a delivery system differs depending on the structure of the carrier (Ibrahim, 1989). Hence, it should be possible to use different phases of liquid crystals in drug delivery though very little work has examined and characterized the nature of the phase structure when liquid crystalline phases were studied. However, it is known that the diffusion of a drug within a liquid crystalline phase differs from that in solution. For example, the diffusion coefficient of a drug within a lamellar phase is approximately one or two orders of magnitude smaller than that in solution, and it has been suggested that liquid crystalline phases, especially the lamellar phase and the hexagonal phase, are potentially very useful systems for topical drug delivery (Lawrence,1994). Topical controlled-release can be achieved if the release rate from the system is less than the diffusion of drug through the skin. It is also possible to achieve a fine tuning of release properties of liquid crystalline systems.

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One approach is to engineer the system to demonstrate phase reversion upon contact with aqueous media since different phases of liquid crystals possess different release patterns. This approach has potential as a sustained-release preparation for intramuscular or subcutaneous administration as well as for rectal application. In these routes of administration, body fluids are expected to serve as an additional component of the system that introduces phase inversion (Lawrence, 1994; Geraghty et al., 1996; Schneeweis and Mueller-Goymann, 1997). The form of the drug present in these systems, either as free acid or base or its salt, may also influence the diffusion of the drug through the thickness of the liquid crystalline layer (Mueller-Goymann and Frank, 1986). Besides controlling drug release patterns, lamellar phase structures are known to exhibit interesting solubility properties in that it is possible to incorporate either hydrophilic, lipophilic, or amphiphilic drugs into the structure (Lawrence, 1994). Some drugs are more soluble in the liquid crystalline phase than in isotropic liquids that have similar composition (Wahlgren et al., 1984).

Table 2 gives some physicochemical properties and potential pharmaceutical applications of various phase structures, including the liquid crystalline phases, of amphiphiles.

7. Evaluation of Drug Release from the Vehicle

In vitro release studies are the primary method to investigate ability of the vehicle to control the performance of a drug delivery system. Selection of an appropriate experimental technique is one of the most crucial steps in obtaining

Table 2. Some physicochemical properties and potential pharmaceutical applications of surfactant phase structure (From Lawrence, 1994)

Phase Structure	Appearance	Viscosity	Solubilization Capacity	Surfactant Concentration	Possible Use
Micelles	Clear, non-birefringent	Low Least viscous phase	Low amphiphilic and non-polar solutes only	0-25%	Solution for most routes of delivery Protection of labile compounds
Cubic Phase	Clear, non-birefringent	Very high Most viscous phase	High amphiphilic and non-polar solutes Low water-soluble solutes	Varies Generally greater 30%	Various preparation for sustained release intramuscular, subcutaneous,oral and topical Protection of labile compounds
Hexagonal	Clear, cloudy birefringent	viscous	Probably high amphiphilic and non-polar solutes Low water-soluble solutes	Wide range possible	Sustained release, particularly topical

Table 2. (continued)

Phase Structure	Appearance	Viscosity	Solubilization Capacity	Surfactant Concentration	Possible Use
Lamellar	Clear, cloudy birefringent	Fairly viscous	Probably high amphiphilic and non-polar solutes Low water-soluble solutes	Wide range possible	Sustained release, particularly topical
Vesicles	Clear, cloudy birefringent	Low viscosity	Probably high amphiphilic and non-polar solutes Low water-soluble solutes	Fairly low Generally less than 10 % by weight	Most routes of administration except oral Protection of labile compounds
Solid	Waxy solid	Stiff	Not known	100 % by weight	Solid dispersion for oral use

accurate data and thus minimizing misleading results. Mathematical modeling of the release data is also necessary in understanding the probable mechanisms by which the carrier has control over the release profile of the system.

7.1 Experimental Techniques (Washington, 1990)

In vitro release methods are the means of assessing the ability of a vehicle or base to liberate medicament under the conditions of the test. Measurement of release profiles requires good sink conditions, so it has been recommended as a rule that the concentration of drug in the release medium must be less than 10% of the saturation concentration of the drug in the medium. This is a useful starting point for experimental design. The total recovery of the drugs into the sink should always be checked in order to discount losses such as degradation of unstable drugs and adsorption of the drug to the apparatus, filters or membranes or other possible routes. If the release profile does not reach 100% at 'infinite' times, then the possibility of experimental errors due to drug loss should be investigated.

A number of experimental methods for the determination of release profiles from vehicle have been used in the past. All of these methods have their advantages and disadvantages that need to be considered before choosing any particular method to investigate drug release.

1. Membrane Diffusion Methods

In this approach, the vehicle is separated from the release medium by dialysis membrane which is permeable to the drug. A diffusion cell is introduced for the study of the transport of a drug within a vehicle. The cell consists of donor and receptor compartments separated by dialysis membrane (Figure 13). The donor compartment contains the vehicle, whereas the receptor phase contains the release medium. The cell is kept at a constant temperature. The drug diffuses out of the vehicle through the membrane to the release medium, and the samples were withdrawn at specific time intervals to be assayed.

Although dialysis membranes have generally been chosen for release studies (Hashida et al., 1980; Benita et al., 1986; Miyazaki wt al.,1986), synthetic membranes such as silicone rubber membranes have also been used (Lalor, Flynn, and Weiner, 1994)

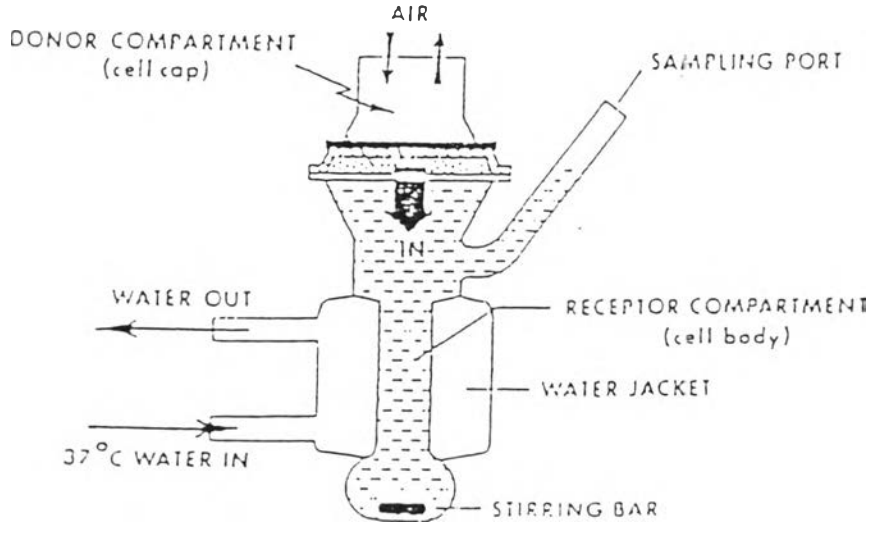

Figure 13. Schematic Representation of Franz Diffusion Cell. (From Chin, 1987)

2. Sampling and Separation Methods

In this experimental setup, the vehicle is diluted into a sink where the concentration of the released drug is assumed to be negligible, and the samples are collected at intervals. The continuous phase of the sample is then separated from the disperse phase, usually by filtration or centrifugation, and the released drug is assayed (Tsukada et al., 1984; Taylor et al., 1990). This type of technique is cumbersome, particularly if the disperse phase consists of very small particles. In this case the particles become difficult to be filtered out or the time needed for sedimentation by centrifugation increases. If the release is fast then it is almost impossible to obtain an accurate release profile.

3. In Situ Methods

In this case the vehicle is directly diluted into a large volume of sink. The released drug is assayed in the sink without separating the residual. In order to do this, a method of assay that is both sensitive and specific to the drug in the solution is required. That is, the assay must be able to discriminate the drug in the solution from the drug in the vehicle without physical separation of the two forms of drug. The major problem is that the response of the drug in the disperse phase can become very large compared to the drug in solution. In this case, lack of an extremely specific assay method may make this experimental setup impractical. This method is specially useful

for liposomal systems when carboxyfluorescein is the model molecule to study release of water-soluble compounds from the vesicle (New, 1990).

4. Continuous Flow Methods

This method allows real-time analysis of drug release, provided that the release half life is sufficiently long. However, the experimentation is rather complicated compared to other methods. In this case, the vehicle is added to a small amount of sink medium contained in a filtration cell (Figure 14). The sink phase is removed through the filter for continuous analysis and then discarded, and fresh sink medium is added to keep the volume constant (Burgess et al., 1987; Koosha et al.,1988). The cell is stirred to prevent the disperse phase from clogging the filter. In practice, variations in flow rate due to filter-clogging can be a problem.

7.2 Mathematical Models of Drug Release (Burrows et al., 1994)

Several mathematical models have been used to describe the release profiles of drugs. Models commonly found in the release studies of drugs from the liquid crystalline system were the following:

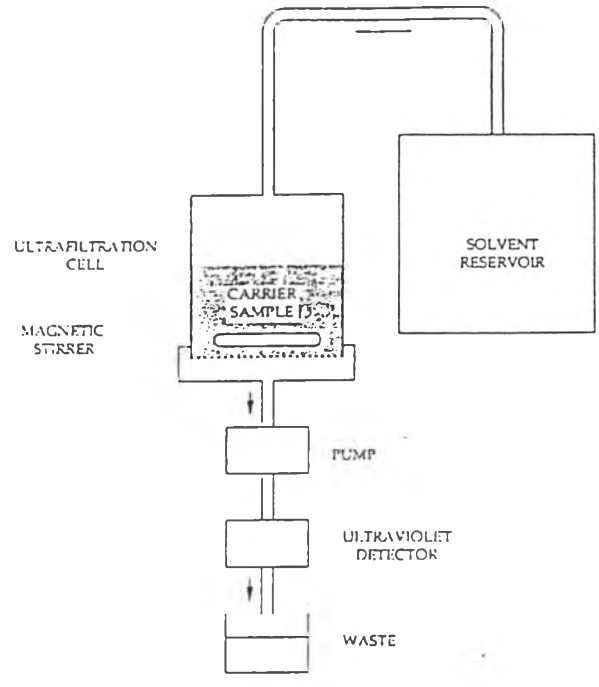

Figure 14. Continuous Flow Drug Release Apparatus. (From Washington, 1990)

7.2.1 Diffusion-Controlled Release

In diffusion-controlled release, the cumulative amount, Q, of drug released per unit surface area of the system is directly proportional to the square root of time, t:

$$Q = kt^{1/2} \qquad (1)$$

where k is a release rate constant.

This model was first introduced by Takeru Higuchi in 1962. Figure 15 illustrates the release profiles of pseudoephedrine hydrochloride and chlorpheniramine maleate which followed the square-root of time relationship over 12 hours, indicating a diffusion-controlled drug release mechanism.

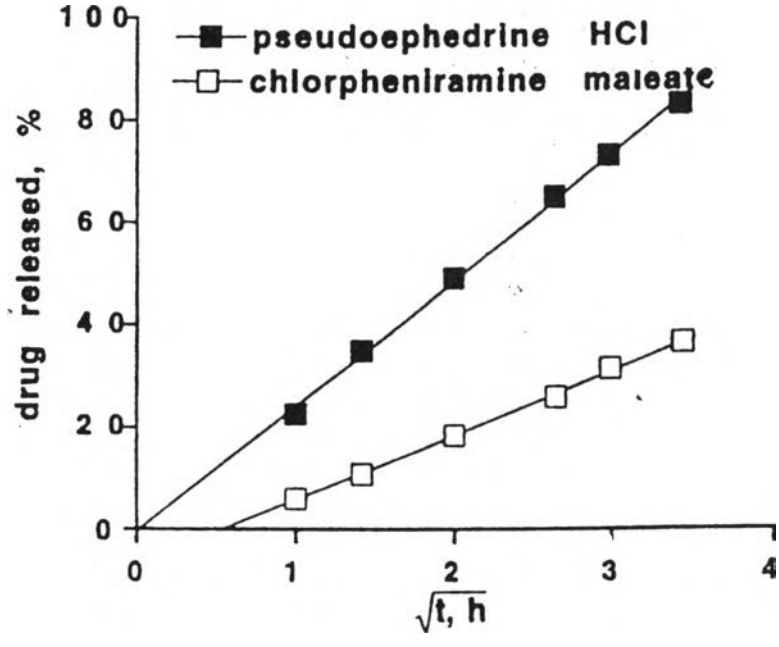

Figure 15. Release Profiles of Pseudoephedrine Hydrochloride and Chlorpheniramine Maleate from Myverol 18-99 Matrices in 0.1 M, pH 7.4 Phosphate Buffer. (From Chang and Bodmeier, 1997)

7.2.2 First-Order Release

This release profile is described by

$$\log (A_0 - Q') = \log A_0 - (k_1 t / 2.303) \qquad (2)$$

where A_0 is the initial amount of drug present, Q' represents the cumulative amount of drug released, k_1 is the first order rate constant, and t denotes the time elapsed from the start of the release. Thus, plots of log amount of drug remaining in the system ($A_0 - Q'$) as a function of time are linear for systems in which drug release conforms to first-order kinetics.

Figure 16 illustrates the release profile of propanolol from a liquid crystalline phase. The release data for this drug can be fitted to equation (2), indicating a first-order release kinetics.

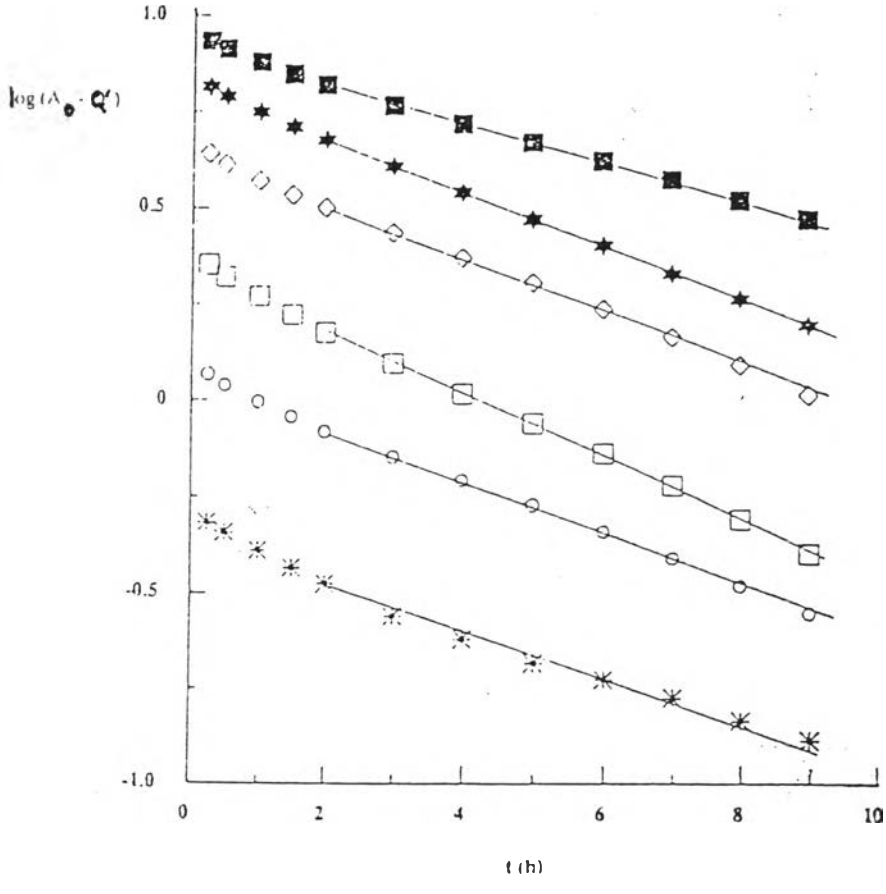

Figure 16. Log Amount of Propanolol Remaining in a Monoolein-Water System as a Function of Time, for Different Initial Drug Loading Concentrations: (*) 1.0%; (o) 2.5%; (□) 5.0%; (◆) 10.0%; (★) 15.0%; (■) 20.0% (From Burrows et al., 1994)