Welcome to Biophysics
(BT 301)

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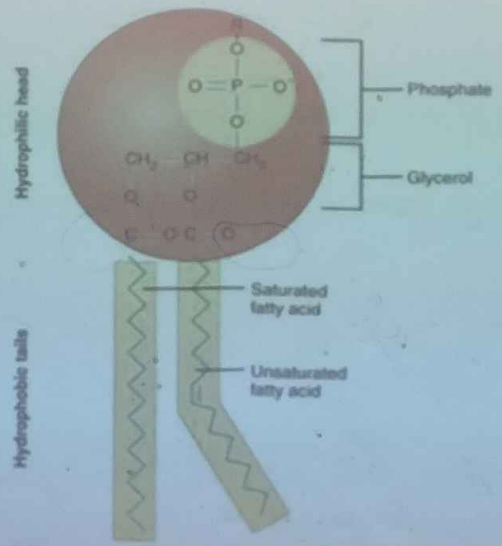
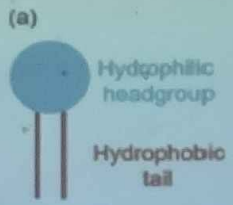
Ack: Few images are from Google

Recap

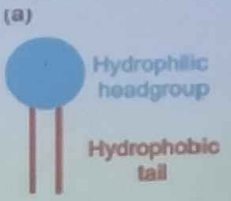

Hydrophilic head
Phosphate
Glycerol
Saturated fatty acid
Unsaturated fatty acid
Hydrophobic tails

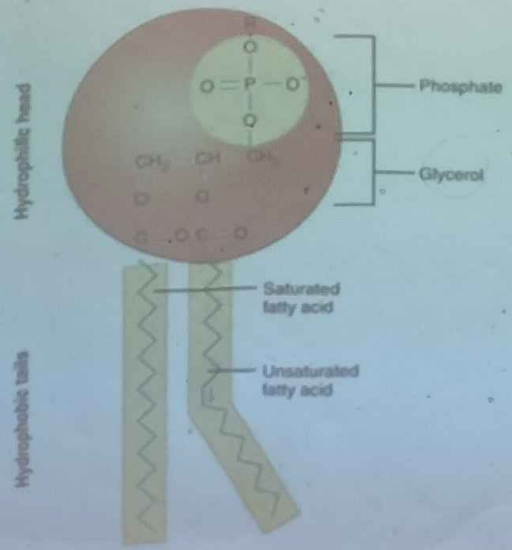

(a)
Hydrophilic headgroup
Hydrophobic tail

Introduction to Lipids

A typical lipid molecule contains a hydrophilic headgroup and two hydrophobic tails (Fig. 1a). The charge of lipids and their chemical properties can be varied by changing the headgroup, while the hydrophobic tails mainly govern the packing in membranes.

Schematic illustration of (a) a lipid.





The tail structures can be changed rendering different phase transition temperatures (T_c). T_c is an important parameter that governs the fluidity of lipid bilayers. Above T_c, lipid tails have gauche conformation and can diffuse more freely, and the membrane exist in a liquid crystalline phase.[28] Below T_c, lipid tails are extended and diffuse slowly, and the membrane is in a gel-like state.

- *Phospholipids are a special group of lipids containing phosphate.*
- *Lipids in general are hydrophobic, also called non-polar. However, the phosphate group in phospholipids is hydrophilic, also called polar.*

RECAP

RECAP

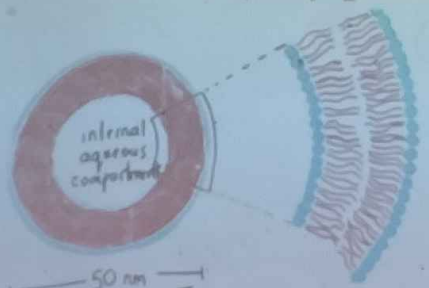
Lipids Connection to Liposomes

Lipids Connection to Liposomes

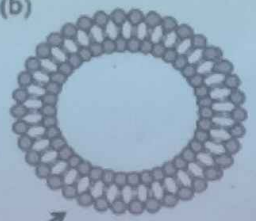
- In addition, we can use the propensity of phospholipids to form membranes to create special structures called liposomes (also called lipid vesicles).

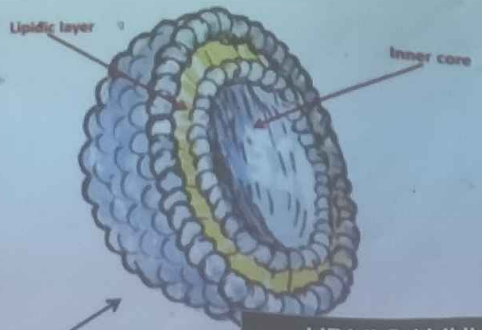
RECAP

Liposomes are small artificial vesicles of spherical shape that can be created from cholesterol and natural non-toxic phospholipids.



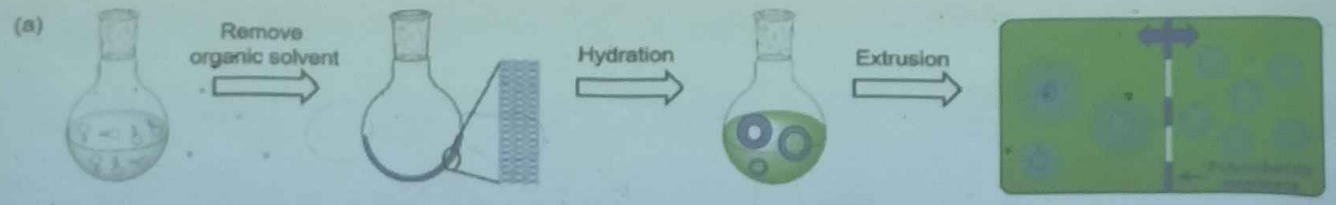
- Liposomes are relatively small (~50 nm in diameter) aqueous compartments that are surrounded by a phospholipid bilayer membrane.



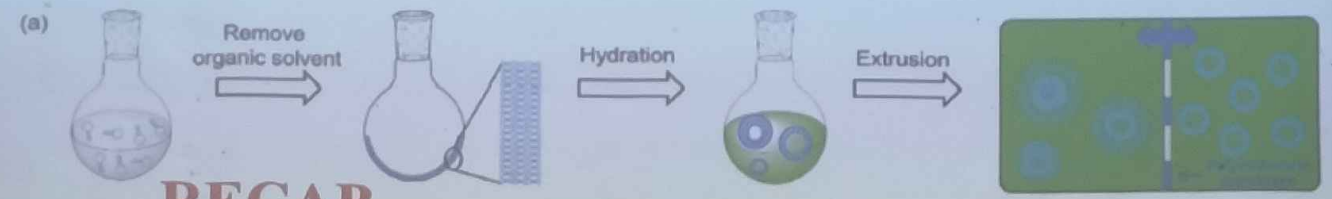


Liposomes illustrated (from different resou

Recap



Formation of Liposomes (Bangham Mtd)

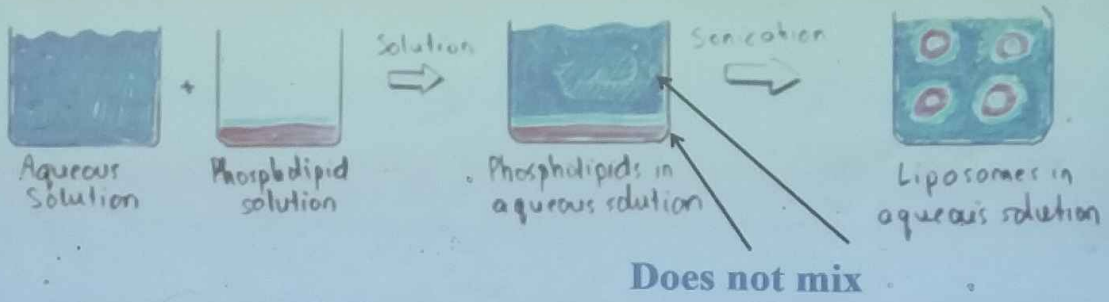


RECAP

(a) Schematic illustration of liposome preparation *via* hydration of dried lipid films followed by extrusion.

The most common Bangham method involves the formation of a lipid film by evaporating the organic solvent used to dissolve lipids.[54] After hydration with an aqueous solution, multilamellar vesicles with a heterogeneous size distribution are formed. By extrusion through a polycarbonate membrane, small unilamellar vesicles (SUVs) with a narrow size distribution are obtained (Fig. 2a). The extrusion temperature needs to be higher than the T_c of the lipids. This method can produce liposomes from ~50 nm to ~200 nm. The larger the membrane pores, the more likely to form multilaminar vesicles.

Formation of Liposomes (Sonification) RECAP



Formation of Liposomes

- Lipid vesicles can be formed by mixing a lipid solution into an aqueous solution and then sonicating the solution. Sonication involves bombarding the solution with sound waves. The energy carried by the sound waves disperses the lipids, allowing them to spontaneously aggregate into bilayer membranes (i.e. liposomes).

MODEL MEMBRANES

A. Biophysical properties of Liposomes
   i. Liposome size
   ii. Liposome fluidity
   iii. Liposome rigidity

B. Active Loading of Liposomes

C. Liposomes and Skin

D. Lipid Monolayer

Acknowledgment: Aggregated Lecture from lot of resource
(Textbook/Journal Papers/Youtube lectures)

Research paper for this lecture

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Targeted liposomal drug delivery: a nanoscience and biophysical perspective

Yibo Liu,[ab] Karla M. Castro Bravo[a] and Juewen Liu *[ab]

Biophysical Properties for Drug delivery (Liposome size)

Biophysical Properties for Drug delivery (Liposome size)

4.1 Liposome size

The size of liposomes is very important for drug delivery.[64] On one hand, it affects the blood circulating time of liposomes.

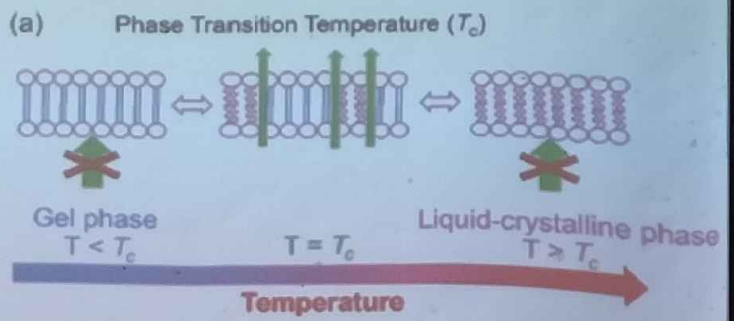
The clearance of nanoparticles and macromolecules in the bloodstream is mediated by the renal system, mononuclear phagocytic system (MPS) or reticuloendothelial system (RES).

Dysfunctional lymphatic drainage in tumors also helps to retain accumulated nanocarriers and allows them to release drugs into the vicinity of tumor cells. Experiments using liposomes of different sizes suggested that the upper threshold for extravasation into tumors was ~400 nm,[68] and other studies have shown that particles smaller than 200 nm were more effective.[19] In comparison, penetration through regular healthy vasculature is limited to 1–2 nm.[69]

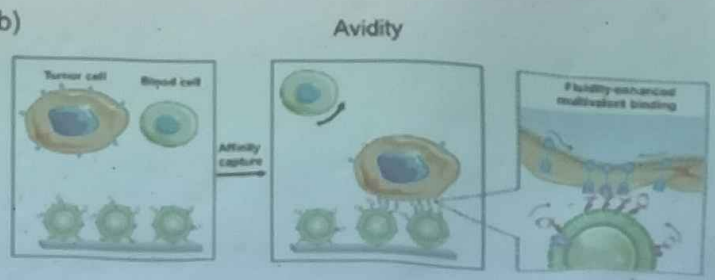
Biophysical Properties for Drug delivery (Liposome fluidity)

Biophysical Properties for Drug delivery (Liposome fluidity)

The structure of lipid tails strongly influences the T_c of lipids, and controls their mechanical strength, lateral diffusion and permeability. The membrane permeability is the largest at T_c because of the coexistence and interconversion of the two phases, creating leaky phase boundaries (Fig. 3a).[78,79] Many thermal-responsive liposomal drug delivery systems have been developed



A distinct feature of lipid membranes compared to inorganic surfaces is surface fluidity, allowing dynamic organization of the anchored ligands.[81–83] Rearrangement of immobilized ligands allows for optimal polyvalent binding, increasing binding affinity (so called avidity for describing polyvalent interactions) (Fig. 3b).[84,85] Tumor targeting by manipulating membrane fluidity was demonstrated in a recent work, with fluid liposomes preferentially targeting the tumor cells and gel-phase liposomes targeting the healthy cells.[86]



Biophysical Properties of Liposomes for Drug delivery

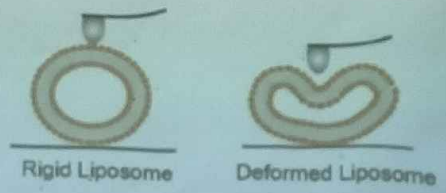
Tc influences rigidity

Biophysical Properties of Liposomes for Drug delivery

Another related factor that can be manipulated to facilitate drug delivery is lipid membrane rigidity or mechanical properties (Fig. 3d). Lipids with a higher T_c afford a more rigid structure with less deformability, while lipids with lower T_c are more flexible. Membrane rigidity influences both cellular uptake and liposome penetration in extracellular matrix (ECM) environment.

(d) Rigidity

Tc influences rigidity.



Desirable Characteristics of Drug Delivery System

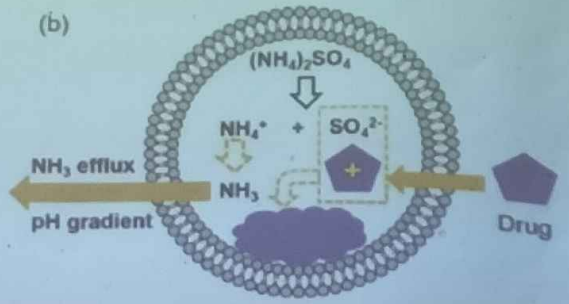
Desirable Characteristics of Drug Delivery System

- *Suitable for delivery of hydrophobic, hydrophilic and amphipathic drugs and agents*
- *Reduce toxicity of encapsulated drug*
- *Non-toxic, flexible, biocompatible, completely biodegradable and non-immunogenic for systemic and non-systemic administration*
- *Biocompatible*
- *Suitable for controlled release*
- *Suitable to give localized action in particular tissues.*
- *Flexibility to couple with site-specific ligands to achieve active targeting*

Liposomes (Active Drug loading)

Liposomes (Active Drug loading)

Active drug loading, also known as remote loading, refers to loading drugs into preformed liposomes. Active loading usually takes advantages of diffusion properties when a pH gradient is established across lipid bilayers.[55] This method requires drugs to have both an uncharged form and a charged form, where only the uncharged drugs can cross liposome membranes. Once diffused into liposomes, they become charged and membrane-impermeable and entrapped inside. The remote loading method has led to the successful development of many commercial formulations.



For Doxil®, a pH gradient was generated by a transmembrane ammonium sulphate gradient. Ammonium salts could dissociate into ammonia and protons. Since ammonia has a high membrane diffusivity, a pH gradient can also be created. Thus, DOX can influx into liposomes and precipitate with ammonium counter ions remained inside to form membrane-impermeable drug complexes (Fig. 2b).[55]

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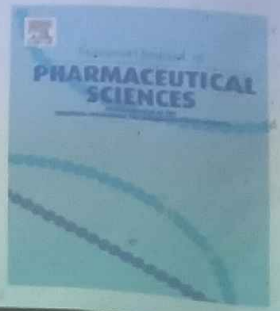


Review

Liposomes and skin: From drug delivery to model membranes

G.M. El Maghraby[a,b], B.W. Barry[c], A.C. Williams[d,*]

Liposomes and skin: From drug delivery to model membranes

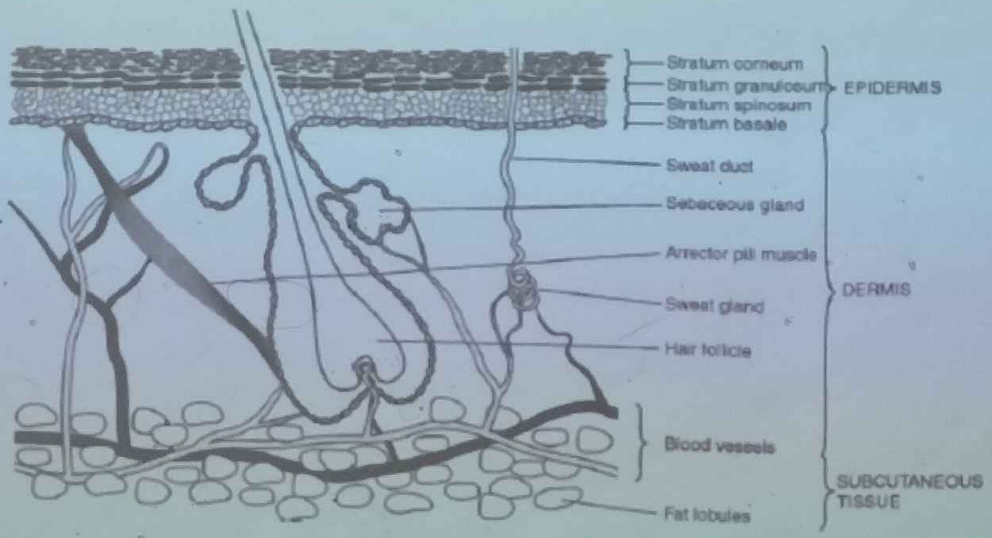


Fig. 1 – A diagrammatical representation of a cross-section through human skin showing the different cell layers and appendages (from Williams, 2003, with permission).

Liposomes and skin: From drug delivery to model membranes

The transepidermal pathway can be defined as the pathway where compounds permeate across the intact, unbroken stratum corneum. This pathway contains two micropathways. First, the intercellular route, which is a continuous but tortuous way through the intercellular lipid domains and secondly, the transcellular pathway through the keratinocytes, then across the intercellular lipids (Fig. 2) (Barry, 1991). As can be seen from Fig. 2, the transcellular pathway requires not only partitioning into and diffusion through the keratin bricks but also into and across the intercellular lipids. Thus, the intercellular lipids play a major role in the barrier nature of the SC.

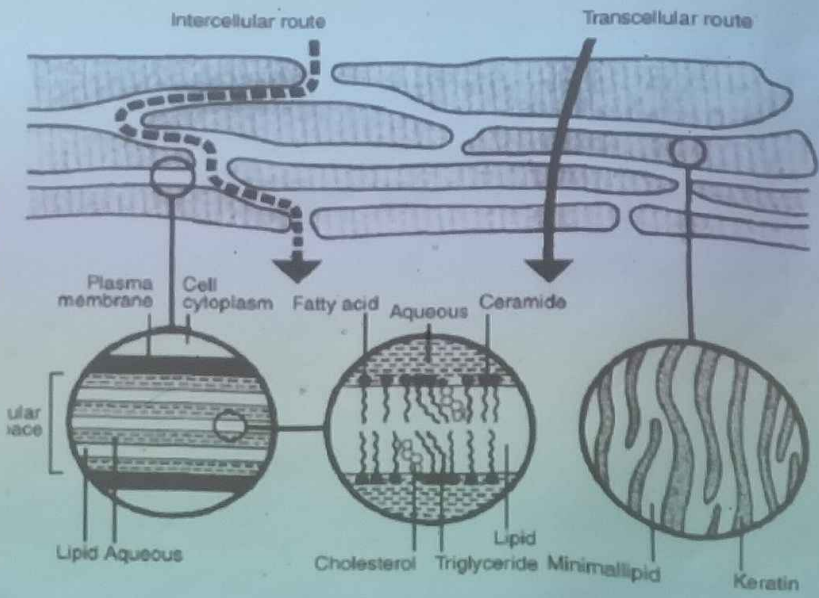
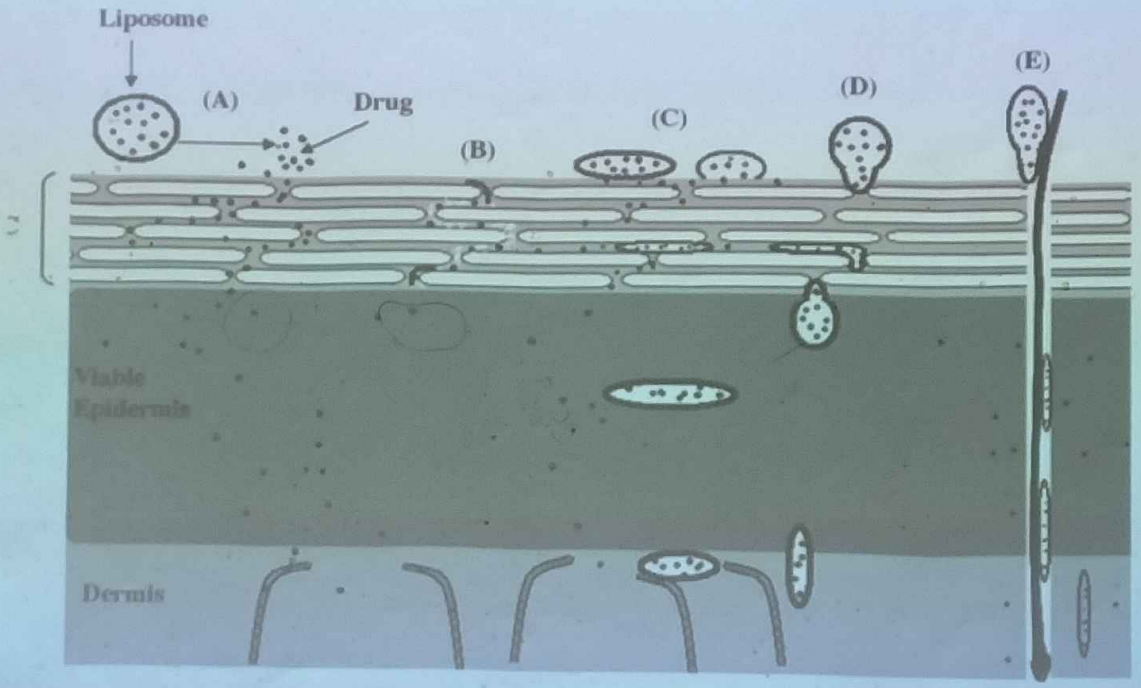


Fig. 2 – Diagram of the brick and mortar model of the stratum corneum with a simplified lamellar organization of intercellular domains showing the major stratum corneum lipids. Also shown are the possible drug permeation pathways through intact stratum corneum; the transcellular or the tortuous intercellular pathways (after Elias, 1981; Barry, 1991).

Fig. 3 – Possible mechanisms of action of liposomes as skin drug delivery systems. (A) is the free drug mechanism, (B) is the penetration enhancing process of liposome components, (C) indicates vesicle adsorption to and/or fusion with the stratum corneum (SC) and (D) illustrates intact vesicle penetration into or into and through the intact skin (not to scale) (modified



Benefits of Drug loading in Liposomes

The benefits of drug load in liposomes, which can be applied as (colloidal) solution, aerosol, or in (semi) solid forms, such as creams and gels, can be summarized into

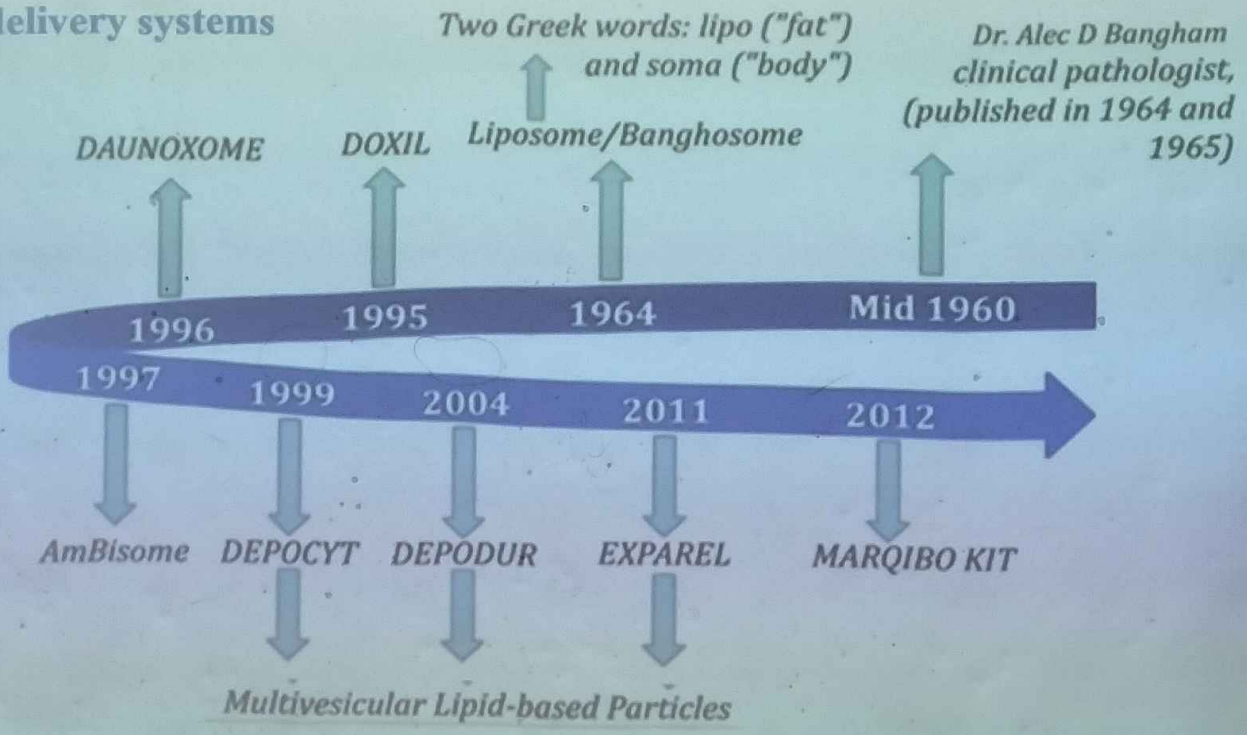
Table 2 Benefits of drug load in liposomes

Benefits of drug load in liposome	Examples
1. Improved solubility of lipophilic and amphiphilic drugs	Amphotericin B, porphyrins, minoxidil, some peptides, and anthracyclines, respectively; hydrophilic drugs, such as anticancer agent doxorubicin or acyclovir
2. Passive targeting to the cells of the immune system, especially cells of the mononuclear phagocytic system	Antimonials, amphotericin B, porphyrins, vaccines, immunomodulators
3. Sustained release system of systemically or locally administered liposomes	Doxorubicin, cytosine arabinoside, cortisones, biological proteins or peptides such as vasopressin
4. Site-avoidance mechanism	Doxorubicin andamphotericin B
5. Site-specific targeting	Anti-inflammatory drugs, anti-cancer, anti-infection
6. Improved transfer of hydrophilic, charged molecules	Antibiotics, chelators, plasmids, and genes
7. Improved penetration into tissues	Corticosteroids, anesthetics, and insulin

Breakthrough Technologies in Liposomes

Breakthrough Technologies in Liposomes

Drug delivery systems



Lipid Monolayer

Lipid Monolayer

Lipid monolayers at the air/water interface offer excellent model systems for various areas in science. They can be used as models to study two-dimensional and surface phenomena in physics and chemistry, such as adsorption, surface activity, wetting, ordering, and phase transitions. In biology, lipid monolayers represent models for biological membranes and biologically important interfaces, such as the gas exchange interface in the lungs and tear film in the eyes.

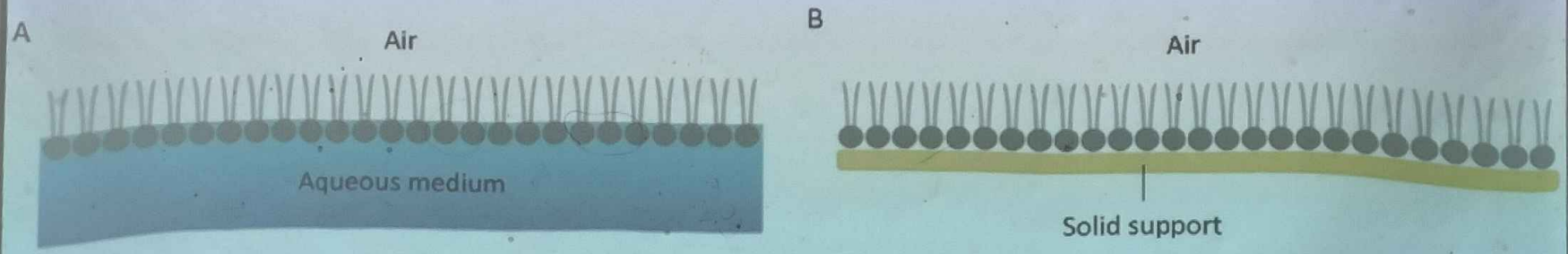


Fig. 1. Schematic representation of a (A) lipid monolayers and (B) solid-supported lipid monolayer.

The properties of lipid monolayers depend dramatically on their molecular density. They can form various phases in two dimensions which are controlled by temperature and by the surface pressure, analogous to the three-dimensional pressure [5].

Modelling LUNG SURFACTANT using Lipid Monolayer

Lipid monolayers can be used as models to study complex phenomena in biological systems. For example, lipid monolayer constitutes the outer layer of tear film in the eyes [22]. Lipid monolayer is the main structural element of lung surfactant, which has very low protein content.

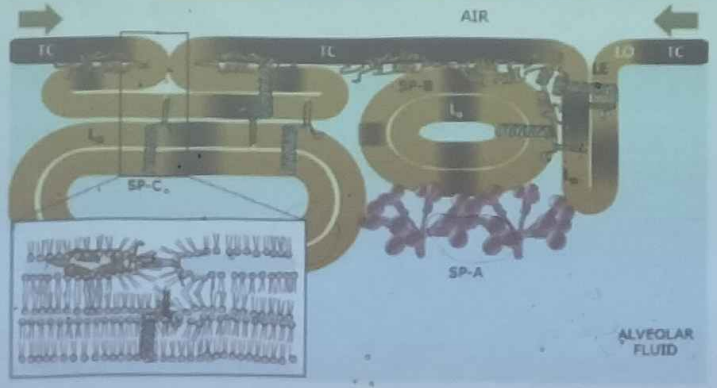


Fig1. 3D structure of lung surfactant.

Lung surfactant is a mixture of lipids and proteins forming a monomolecular film at the gas exchange interface in the lung alveoli [8]. Lung surfactant facilitates breathing. Its deficiency or inhibition causes failure of lung function that leads to severe respiratory disorders.

Lung surfactant consists mainly of PC lipids (80% by weight), with DPPC as major component (40% w). Anionic PG and PI lipids account for 8–15% by weight. Lung surfactant also contains cholesterol (5–10% w), PE lipids, fatty acids, and other minor components. Overall, lung surfactant is characterized by a rather complex lipid composition.