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Nanotechnologies — Vocabulary — Liposomes

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Foreword

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~~The committee responsible for~~ This document ~~is ISO/~~was prepared by Technical Committee TC 229, *Nanotechnologies*.

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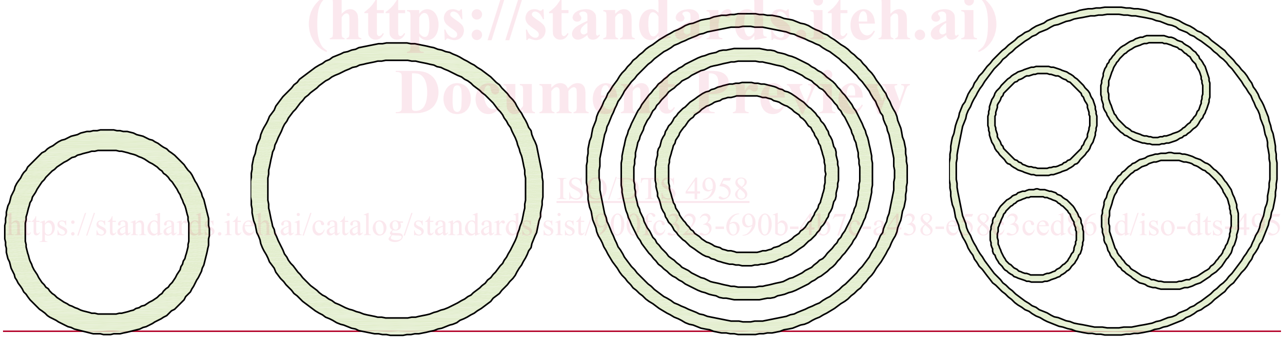
Introduction

Lipid-based nanomaterials represent an important class of carriers for the in vivo transport and delivery of active pharmaceutical ingredients (APIs). By encapsulating the API inside a lipid-based structure, payloads can be protected from degradation while potent APIs can be delivered with reduced adverse physiological effects. These lipid-based carriers are carefully formulated to achieve specific properties and are generally well tolerated and biocompatible.

Lipid particles include different structural forms or subclasses that can be differentiated by structure, composition and chemistry (e.g., liposomes, solid lipid nanoparticles). The first lipid-based nanomaterial product to obtain regulatory approval in the US and EU was liposomal doxorubicin, approved in 1995 in the US for the treatment of ovarian cancer and AIDS-related Kaposi sarcoma. More recently, cationic lipid-containing nanoparticles complexed with mRNA were formulated as highly effective vaccines against the coronavirus SARS-CoV-2. ~~The present~~This document aims to standardize the terminology associated with the most studied and mature form of lipid-based carriers, namely liposomes.

Liposomes are synthetic vesicles composed of a single bilayer (most common form for drug delivery) or of multiple concentric or non-concentric bilayers separated by aqueous compartments. Figure 1 schematically illustrates these basic structural forms of liposome as used within ~~in~~ a biomedical context.[‡] An example of pharmaceutical relevance (e.g., a drug product) is provided for each vesicle form defined in ~~section 3.2 of this document~~3.2.



~~1~~ ~~2~~ ~~3~~ ~~4~~

~~**Key**~~

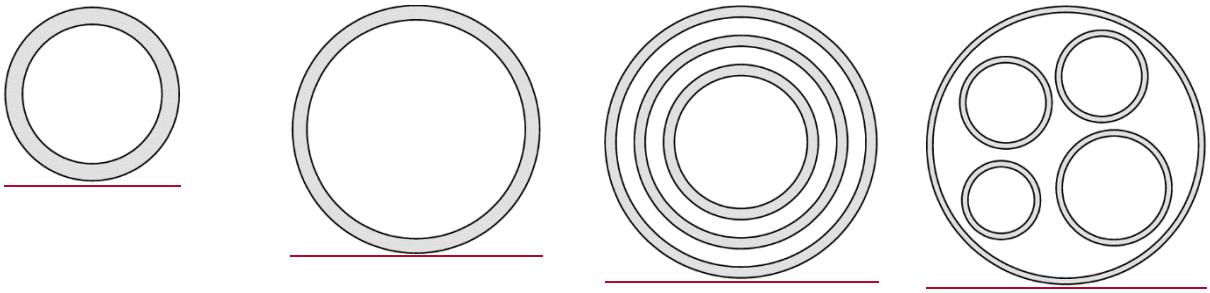
~~1 small unilamellar vesicle (SUV), ≤ 100 nm~~

~~2 large unilamellar vesicle (LUV), > 100 nm~~

~~3 multilamellar vesicle (MLV), ≥ 500 nm~~

~~4. multivesicular liposome (MVL), > 1000 nm~~

[†] Graphics courtesy of Scientific Publications, Graphics and Media, Frederick National Laboratory for Cancer Research



a) Small unilamellar vesicle ≤100 nm | b) Large unilamellar vesicle >100 nm | c) Multilamellar vesicle ≥500 nm | d) Multivesicular liposome >1 000 nm

NOTE Images are not drawn to scale.

SOURCE: Scientific Publications, Graphics and Media, Frederick National Laboratory for Cancer Research.

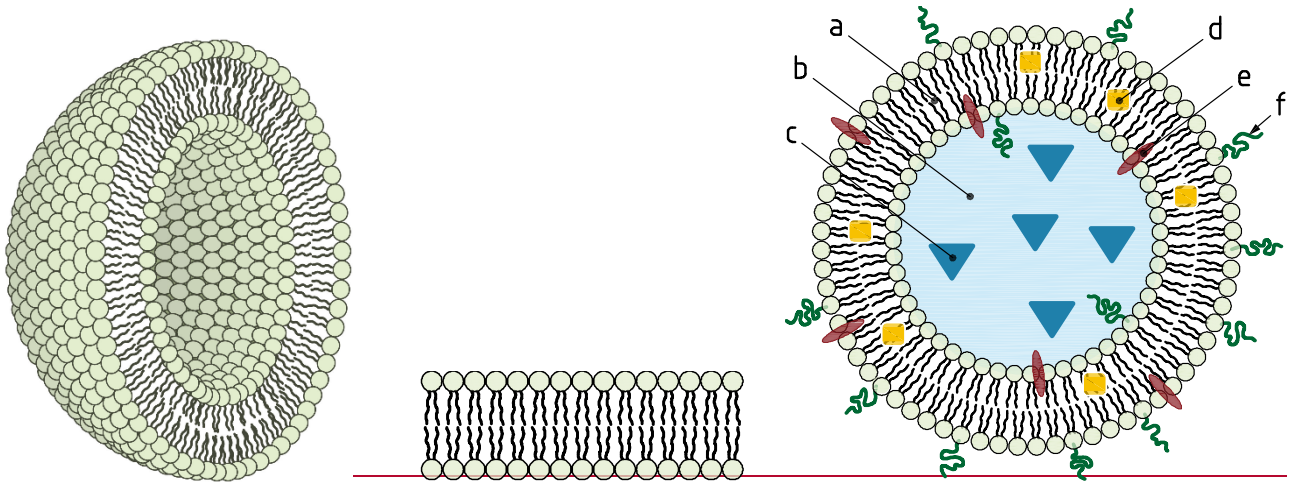
Figure 1 — Schematic illustration showing lamellar structure of different vesicle types~~. Images not drawn to scale.~~

The bilayers are formed by amphipathic molecules, primarily phospholipids, but can include other molecular components necessary for membrane integrity (e.g~~.~~ cholesterol) or avoidance of opsonization and reticuloendothelial clearance ~~(~~[e.g~~.~~ polyethylene glycol ~~—~~(PEG~~).~~)].

The size of liposomes can range from approximately 20 nm to over ~~1000~~1 000 nm, though therapeutic delivery most commonly involves particles in the 50 nm to 200 nm diameter range. Therefore, while not all liposomes are nano-objects as defined ~~by ISO~~in this document, all liposomes consist of bilayers of nanoscale thickness and are therefore generally considered both nanomaterials and nanostructured materials.

~~The cartoons in~~ Figure 2 depict a 3D cross-sectional perspective of an idealized unilamellar liposome, a lipid bilayer and a liposomal drug formulation showing the location of compartments and APIs.

Figure 3 illustrates the three principal structural phases associated with lipid bilayers. These phases are principally dependent on composition and temperature, but other factors such as pH can also play a role.



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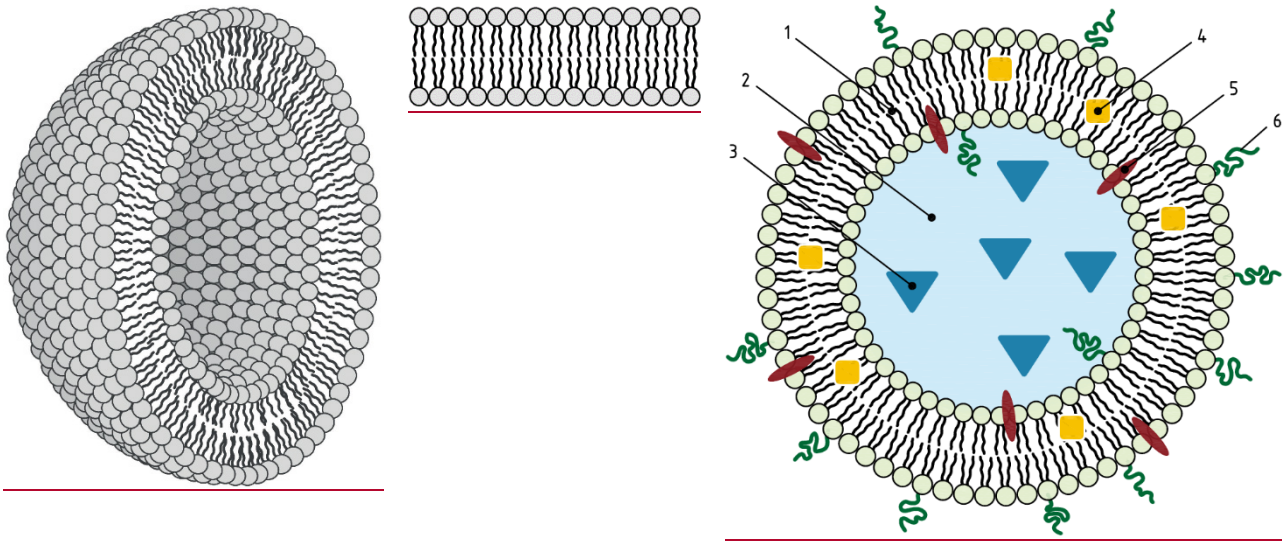


a) 3D hemispherical view | b) Cross-section of bilayer segment | c) Liposome cross-section showing bilayer with details

Key

~~1 3D hemispherical view~~

1 hydrophobic compartment (lipid bilayer)
2 hydrophilic compartment (aqueous phase core)
3 hydrophilic active pharmaceutical ingredient (API)
4 hydrophobic API
5 amphiphilic API
6 polyethylene glycol (PEG)

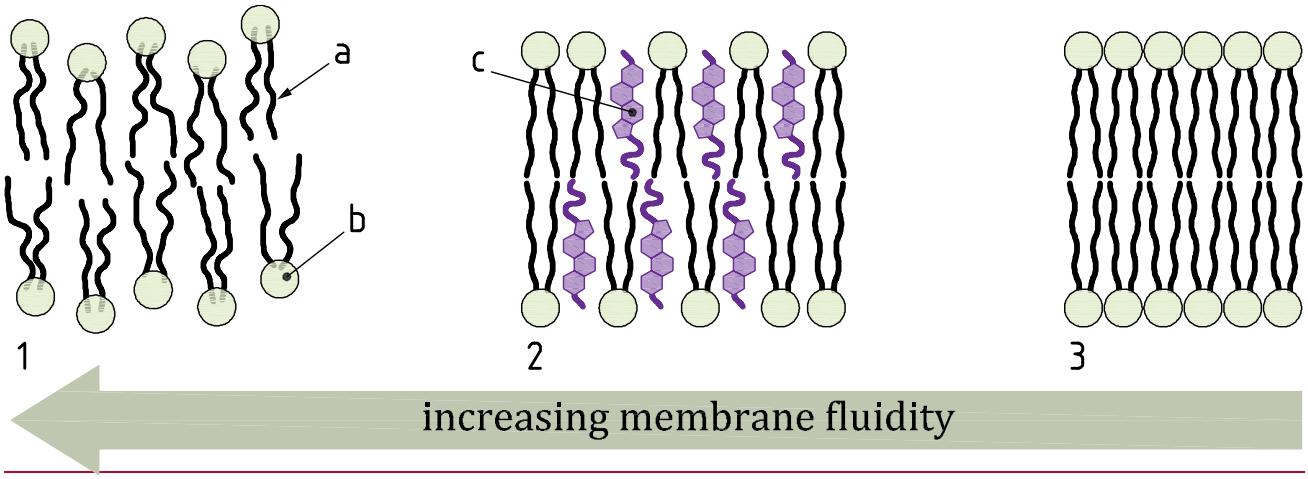
NOTE 1 Images are not drawn to scale.

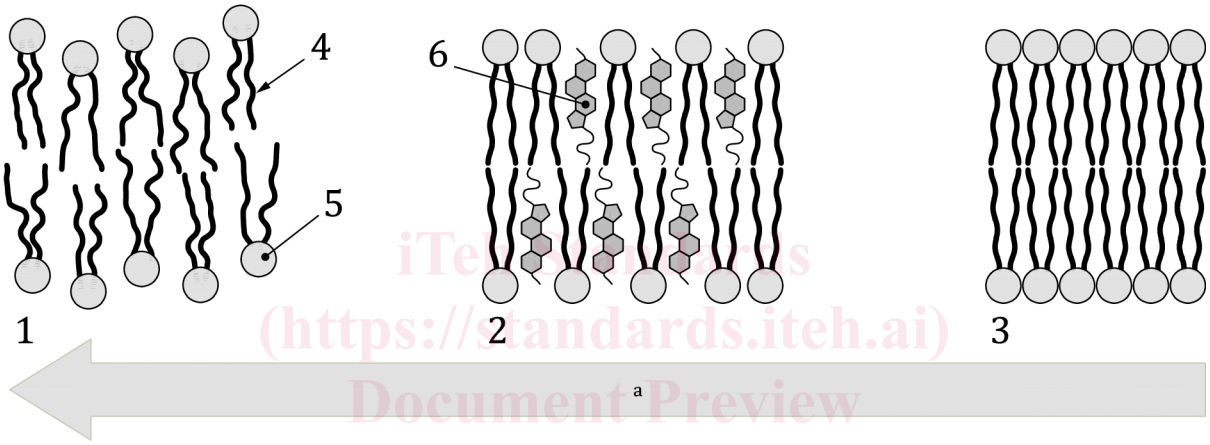
NOTE 2 ~~cross-section of bilayer segment (~~ In Figure 2 b), polar headgroups are shown in green ~~–~~and hydrophobic tails are shown in black~~).~~

~~3 liposome cross-section showing bilayer with details~~
~~a hydrophobic compartment (lipid bilayer)~~
~~b hydrophilic compartment (aqueous phase core)~~
~~c hydrophilic active pharmaceutical ingredient (API)~~
~~d hydrophobic API~~
~~e amphiphilic API~~
~~f polyethylene glycol (PEG)~~

SOURCE: Scientific Publications, Graphics and Media, Frederick National Laboratory for Cancer Research.

Figure 2 — Idealized unilamellar liposome showing phospholipid bilayer structure, internal compartments~~,~~ and representative details~~. Images not drawn to scale~~





Key

~~1 liquid disordered phase (above phase transition temperature)~~
~~2 liquid ordered phase (induced by cholesterol)~~
~~3 gel phase (below phase transition temperature)~~
~~a phospholipid fatty acid tails~~
~~b phospholipid polar headgroup~~
~~c cholesterol~~

1 liquid disordered phase (above phase transition temperature)
2 liquid ordered phase (induced by cholesterol)
3 gel phase (below phase transition temperature)
4 phospholipid fatty acid tails
5 phospholipid polar headgroup
6 cholesterol
[a] Increasing membrane fluidity.

NOTE Images are not drawn to scale.

SOURCE: Scientific Publications, Graphics and Media, Frederick National Laboratory for Cancer Research.

Figure 3 — Idealized illustration of phospholipid bilayer structural phases~~. Images not drawn to scale.~~

~~Because of~~Due to their versatile nature, liposomes are promising materials in many industrial fields. In addition to therapeutics, liposome technologies are applied in cosmetics and dietary supplements, for example.

~~The bibliography provides a list of sources and consultative published documents used in the development of this technical specification.~~ Additional terms ~~and definitions~~ that relate to the nano~~/~~- or bio- ~~interface~~-interfaces and nanotechnologies related to diagnostics and therapeutics for healthcare are ~~provided~~defined in ISO/TS 80004-5 and ISO/TS 80004-7, respectively.