

## Chapter 2

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# Liposomes as drug delivery system

Literature covering the components, classification, as well as the advantages and disadvantages of liposomes as a drug delivery system.

## 2.1. Introduction

The term liposomes covers a very large number of different structures, but it can be defined as a lipid bilayer structure or a membrane that encloses an internal aqueous volume. The structure of the membrane can vary significantly, making it possible to create a vast amount of different liposomes, each with their own characteristics and applications. When this system is used for drug delivery, both hydrophilic and lipophilic drugs can be transported therein (Torchilin, 2007).

Liposomes were first described in 1964 by A.D. Bangham and his colleague R.W. Thorne after examining and analysing a dispersion of phospholipids in water under an electron microscope (Betageri *et al.*, 1993). They found that the phospholipids automatically arranged themselves to form structures that they referred to as “bag-like”. A close colleague, Gerald Weissman, suggested the structures be called liposomes, which he then defined as “microscopic vesicles composed of one or more lipid bilayers”. This discovery led the way to a large field of research. The uses found for liposomes have been wide-spread and even include drug delivery systems for cosmetics (Deamer, 2010).

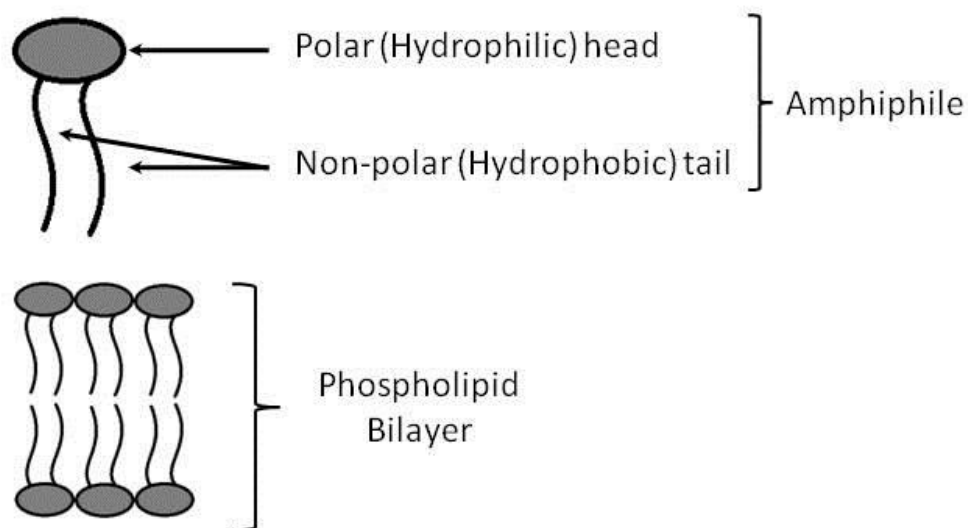
The main reason why research into liposomes advanced as it has, can be largely attributed to the fact that liposomes can mimic biological cells. This also means that liposomes are highly biocompatible, making them an ideal candidate for a drug delivery system, with applications ranging from delivering enzymes, antibacterials, antiviral drugs, antiparasite drugs, fungicides, transdermal transporters, diagnostic tools and adjuvants for vaccines (Lasic, 1998).

## 2.2. Components of liposome structure

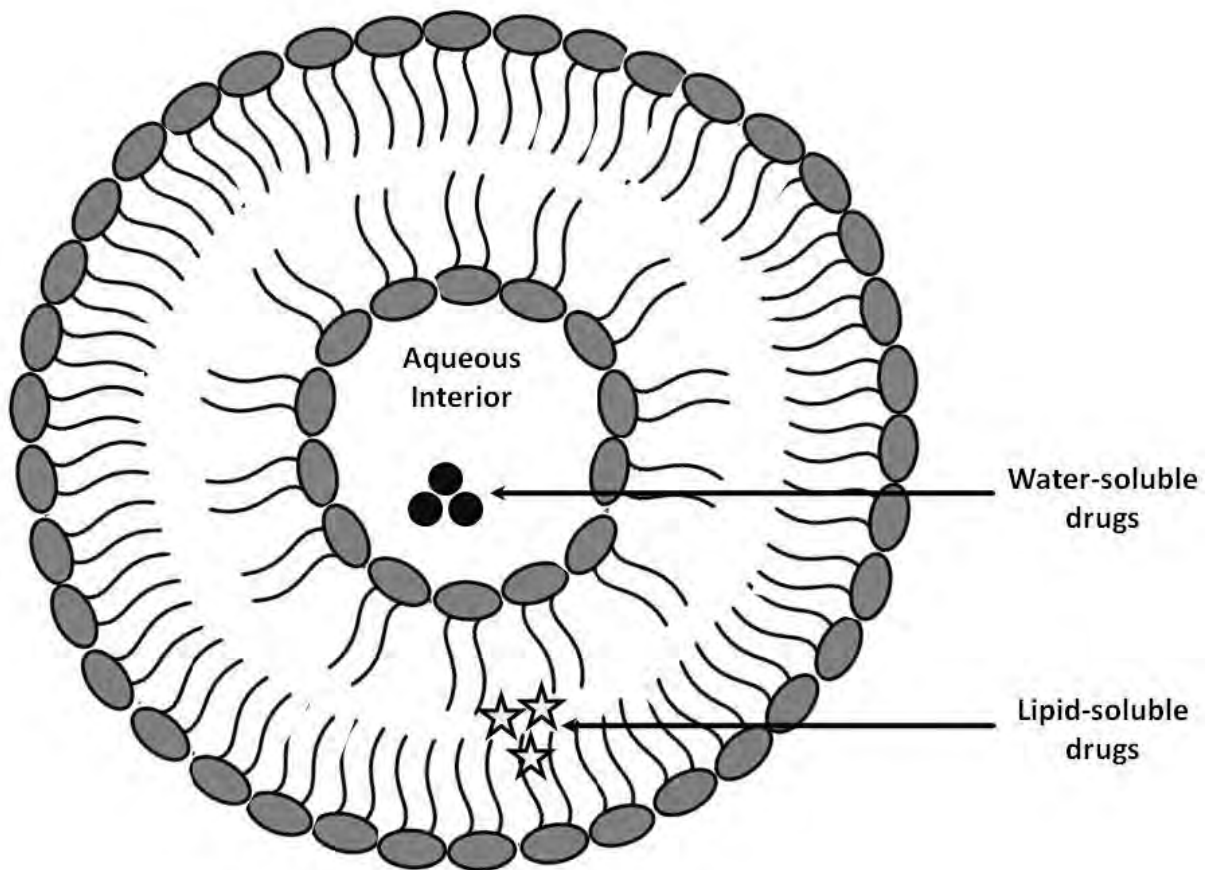
Liposomes are versatile in that the entire membrane of the liposome can be composed of either natural or man-made phospholipids. The properties of the liposomes can be changed entirely depending on the phospholipids used. The basic components of liposomes are phospholipids which are stabilised by cholesterol, with other stabilisers sometimes added to the mixture depending on the specific use of the liposome. Many different types of lipids and lipid mixtures can be used or mixed-and-matched to obtain a certain type of liposome (New, 1990).

### 2.2.1. Phospholipids

The structure of the phospholipids are as follows: on the one end of the molecule are the hydrophobic acyl hydrocarbon chains. The other end of the molecule, which is also called the phosphate head group, is hydrophilic. This molecule is not as such water soluble but rather, the molecules aggregate and align automatically in a planar bilayer form. The basic structure of lipids is illustrated in Figure 2.1. In this way the hydrophobic parts of the molecule are kept from water and the hydrophilic part of the molecule can interact (New, 1990). The double fatty acid chains interaction with one another are also thought to help create the round shape which these molecules form naturally (Roerdink *et al.*, 1987). The complete liposome structure can be seen in Figure 2.2.

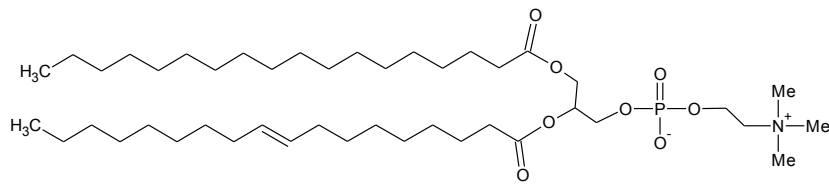


**Figure 2.1: Illustration of the basic elements of a lipid, with the arrangement into the lipid bilayer structure. As adapted from Blomme, 2008.**

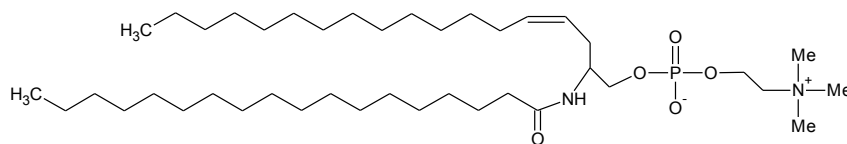


**Figure 2.2: Illustration of the basic form the lipid bilayer forms in an aqueous solution. The position of the drugs formulated into liposomes is also displayed. As adapted from Blomme, 2008.**

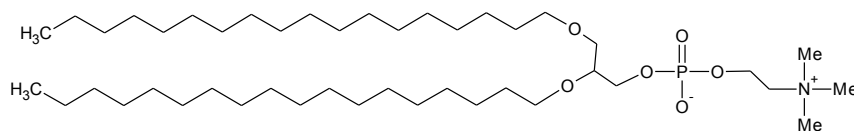
Lipids all have a temperature at which their fluidity changes. This temperature is also known as transition temperature ( $T_C$ ). The  $T_C$  is directly proportional to the length of the acyl chain; the longer the chain, the higher the  $T_C$  and the more rigid the membrane. The rigidity of the membrane is also responsible for better stability. More rigid membranes keep entrapped drugs inside, or in other words, prevent leakage (Sharma & Sharma, 1997). The  $T_C$  is very important, as it can affect the way the membrane reacts to fusing with other liposomes, aggregation, stability, permeability as well as contributing to the way the liposomes react in the presence of biological systems (New, 1990). The main classes of choline containing lipids are illustrated in Figure 2.3.



**Phosphatidyl choline, also known as lecithin**  
1,2-diacyl-sn-glycerol-3-phosphoryl choline



**Spingomyelin**  
N-acyl-trans-4sphingenine-1-phosphoryl choline



**Phosphatidyl choline linked by ether**  
1,2 dialkyl-sn-glycerol-3-phosphoryl choline

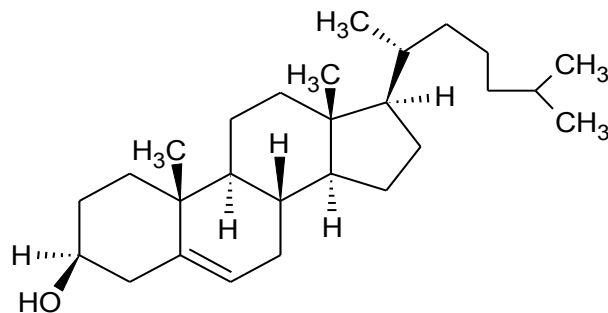
**Figure 2.3: The main classes of phospholipids that contain choline. As adapted from New (1990).**

### 2.2.1.1. Phosphatidylcholines

Phospholipids containing the choline group are one of the most abundant lipids in nature. The phospholipid most often used for liposomes is the phospholipid known as phosphatidylcholine (PC). PC is often referred to as lecithin. This phospholipid is very popular because of its relative low cost and general tendency to be neutral (New, 1990). PC is procured from natural sources, plants with soybeans as an example, and mammalian sources such as bovine heart, spinal column or in some cases from egg yolk. PC gives the membrane rigidity. The structure of the specific lipid provides the fluidity as well as bilayer strength. These factors are dependent on the amount of saturation as well as the length of the hydrocarbon chain (Betageri *et al.*, 1993).

### 2.2.2. Cholesterol

One of the other components normally included into the membrane of liposomes is cholesterol. The structure of cholesterol can be seen in Figure 2.4. Cholesterol on its own does not in fact create the specific recognisable bilayer structure. When cholesterol is added into the mixture the cholesterol stabilises the liposomes, or in other words, it increases the  $T_C$  of the membrane. The addition of cholesterol decreases the permeability of the bilayer, thus helping to keep the liposome stable and to keep the intended drug entrapped (New, 1990). Cholesterol incorporation into membranes is also important for it was found that liposomes without cholesterol released the entrapped drug prematurely and this is accelerated further when liposomes are confronted with high density lipo-proteins, which take up the phospholipids. Cholesterol is thought to interfere with this process, which in turn stabilises the entire membrane of the liposome (Kirby *et al.*, 1980).



**Figure 2.4: The chemical structure of cholesterol**

### 2.3. Classification of liposomes

Many different methods can be employed to classify liposomes, with size and structure being the most widely used. The classification was first agreed upon at a meeting of the New York Academy of Science which was titled "Liposomes and Their Uses in Biology and Medicine". The classification uses three letter acronyms to name the different classes (Betageri *et al.*, 1993). Other classifications that are used are classification according to production methods as well as classification according to the composition of the liposomes

#### 2.3.1. Characterisation of liposome according to size and shape

- **Multilamellar Vesicles (MLVs).** These liposomes have more than one lamella, and can vary in size between 100 to 1000nm.

- **Small Unilamellar Vesicles (SUVs).** These liposomes are smaller than 0.1µm with just a single lamella. The composition of the membrane, as well as the aqueous medium has an influence on the minimum size that can be attained. The size variation of the population of SUVs is small when the liposomes approach the minimum size.
- **Large Unilamellar Vesicles (LUVs).** These liposomes sizes start from 0.1µm and can reach sizes of up to 1000nm, which is close to the size of living cells. These liposomes have just a single lamella.

### 2.3.2. Classification of liposomes according to composition

The membrane of liposomes is normally constituted of natural components found in the membranes of regular living cells, but these constituents can be widely varied and may even include synthetic materials. Just tweaking the proportions of the ingredients can change the properties of the membrane as well as the uses available to the manufacturer.

- **Conventional liposomes**

These liposomes are composed of natural phospholipids (which may be neutral or negatively charged) and cholesterol. These liposomes are often used for targeting of the reticulo-endothelial system (RES). This shortens the circulation times of the liposomes substantially. Contents of these liposomes are most often destined for lysosomes (New, 1990).

- **pH-sensitive liposomes**

The membranes of these liposomes are composed of either cholesterol hemisuccinate (CHEMS), phosphatidyl ethanolamine (PE), oleic acid (OA) or dioleoylphosphatidyl ethanolamine (DOPE). These liposomes fuse with cells when the pH is low, thus releasing its content into the cell cytoplasm. These liposomes are ideal for the delivery of macromolecules and weak bases (Sharma & Sharma, 1997).

- **Cationic liposomes**

Cationic lipids make up the membrane of these liposomes with dimethyl-dioctadecyl ammonium bromide (DDAB), dioctadecyldimethyl ammonium chloride (DOGS), 2,3-dioleoyloxy- N - ( 2 (spermine carboxamido) - ethyl) - N, N-dimethyl - I - propanaminium fluoracetate (DOSPA), 1,2 dioleoyloxy-3-(trimethylammonio) propane (DOTAP), 1,2dimrystyloxypropyl-3-dimethyl-hydroxyethyl ammonium bromide (DMRIE), and 1,2-dioleoyloxypropyl-3-dimethyl-hydroxyethyl ammonium bromide (DORIE) combined with dioleoylphosphatidyl ethanolamine (DOPE). These liposomes tend to be toxic in high doses with a short lifespan, thus restricting them to local administration. They are most

often used for the delivery of macro molecules that have a negative charge, this includes the delivery of DNA and RNA (New, 1990).

- **Long-circulating Liposomes (LCL)**

The lipids used for this type of formulation are neutral lipids with a high  $T_C$ . Cholesterol is also included in these formulations (normally between 5 and 10%). These liposomes have a very long circulation half life, of up to 40 hours (Sharma & Sharma, 1997).

- **Immuno-liposomes**

These liposomes are Conventional liposomes (CL) or Long Circulating Liposomes (LCL) with antibody or other recognition sequences attached to the surface. These liposomes are formulated to bind to specific cells and to release the drug in that area, thus making it a targeted delivery system (Sharma & Sharma, 1997).

### 2.3.3. Classification of liposomes according to production method

Figure 2.5 illustrates a simplified diagram of how the different production methods come together, as well as the products produced by the method.

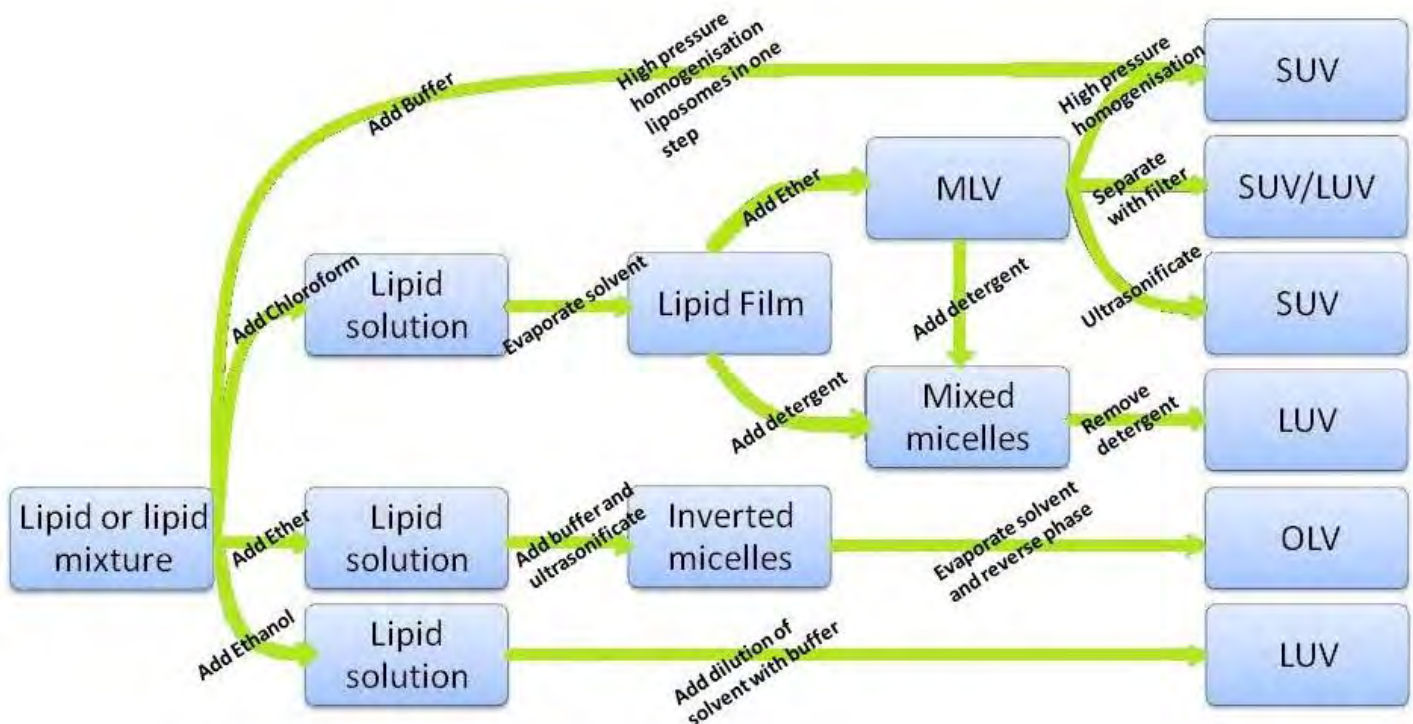


Figure 2.5: A simplified illustration production methods of Liposomes, as adapted from Müller et al., 1998.

### 2.3.3.1. Mechanical dispersion methods

These methods basically involve drying lipids onto a surface and then adding the aqueous phase. The lipid is then moved from the surface using mechanical methods (which is shaking in most cases) when an aqueous phase is added. Methods in this class are the following:

- Hand-shaken multilamellar vesicles (MLVs).
- Non-shaken vesicles.
- Pro-liposomes.
- Freeze drying.
- Processing of lipids hydrated by physical means.
- Micro-emulsification liposomes (MEL).
- Sonicated vesicles.
- French pressure cell liposomes.
- Membrane extrusion liposomes.
- Dried reconstituted vesicles (DRVs).
- Freeze-thaw sonication (FTS) method.
- pH-induced vesiculation.
- Calcium-induced fusion to produce large Unilamellar vesicles (New, 1990).

### 2.3.3.2. Solvent dispersion methods

These methods can be summarised as dissolving the lipids and other constituents of the liposome's membrane in an organic solution. The resulting solution is then added to the aqueous phase. The aqueous phase normally contains the material which is to be entrapped. Methods in this category are the following:

- Ethanol injection.
- Ether injection.
- Water-in-organic phase.

Each of the above-mentioned have many other specific methods which are classified under them, but the basic thought behind them is the same (New, 1990).

### 2.3.3.3. Detergent solubilisation

Production methods in this class involve using an intermediary detergent when adding the phospholipids to the aqueous phase. The intermediary detergent helps to bring the phospholipids in close contact with the aqueous phase, but still protects the hydrophilic part of the phospholipid. These intermediaries are often soluble in both aqueous and organic solutions. This method then creates micelles. The specific names of the methods in this class are as follow:

- Bile salt preparation.
- Alkyl glycoside dialysis.
- Triton X-100 solubilised Sendai virus particles (New, 1990).

## 2.4. Advantages of Liposomal drug delivery

Currently, there are quite a few drugs on the market that are used only in the direst situations, often because of severe side-effects and toxicity. Many of these drugs have exceptional antimicrobial effect, but the poor pharmacokinetic and pharmacodynamic properties limit their use. Drug encapsulation in a liposomal or lipid drug delivery system can improve the above-mentioned problems to such an extent that the drugs can be brought into regular use as the pharmacokinetic and pharmacodynamic properties can be controlled (Bakker-Woudenberg, 2002; Drulis-Kawa & Dorotkiewicz-Jach, 2010). The advantages of liposomes as a drug delivery system for antimicrobials are:

- Improvement and control over pharmacokinetics and pharmacodynamics.
- Decreased toxicity.
- Enhanced activity of drugs against intracellular pathogens.
- Liposomes can be made to be target selective.
- Enhanced activity against extracellular pathogens (Drulis-Kawa & Dorotkiewicz-Jach, 2010).

### 2.4.1. Improvement of pharmacokinetics and pharmacodynamics

Many drugs require regular doses when given without a drug delivery system. Liposomes can be formulated to have a long circulating time, thereby keeping drug levels constant for longer periods. The ways in which circulation time can be increased are by using neutral lipids with a high  $T_C$  value or by coating liposomes with polyethylene glycol (PEG), and thus creating so

called “Stealth” liposomes (Bakker-Woudenberg, 2002). Factors that influence the circulation time are: the fluidity of the membrane, the size of the liposomes (smaller liposomes circulate longer) and the charge on the liposomes (neutral liposomes have a long circulation time). Liposomes are able to protect certain drugs against chemical and immunological breakdown, as well as protecting them against the effect of some enzymes (Omri & Ravaoarino, 1996). Liposomes can give lowered toxicity and lower dosing because of sustained drug levels, especially when so called “stealth” liposomes are used (Drulis-Kawa & Dorotkiewicz-Jach, 2010).

#### **2.4.2. Liposomes can be made target selective**

Cells react to other cells according to the structure and make-up of the cell membranes. This can be exploited for drug targeting by inducing specific cells to react to, and absorb the liposomes. The structure of the membrane surface can be widely modified for specific drug targeting; by either changing the charge of the membrane (Kim *et al.*, 1999), or adding specific proteins, antibodies or immunoglobulin. This increases the specific cells affinity to the liposomes. Other techniques that have been experimented with include: creating liposomes that react to specific pH's, or temperatures, before releasing the drug (Drulis-Kawa & Dorotkiewicz-Jach, 2010). Liposomes can be made to just interact with specific organisms (Robinson *et al.*, 2001; Kim *et al.*, 1999). In an attempt to lower toxicity, liposomes can in certain rare cases be made to avoid certain areas. This is known as site-avoidance-therapy (Storm & Crommelin, 1998; Sharma & Sharma, 1997)

#### **2.4.3. Enhanced activity of drugs against intracellular pathogens**

Liposome formulations have been tested for many years against an entire host of intracellular parasites and other pathogens. Liposomes have been used to great success in the treatment of leishmaniasis as the liposomes used to treat the *Leishmania* are actively removed *in vivo* by the macrophages which are infected by *Leishmania*. The encapsulated drug was 700 times more effective than the free drug in the treatment of *Leishmania* in hamsters (Alving *et al.*, 1978). These findings were followed up by a whole host of other studies that confirmed these types of successes with leishmaniasis (Date *et al.*, 2007).

In studies of anti-tuberculosis drugs like clarithromycin, isoniazid and rifampicin, the efficacy of each drug was significantly higher when compared to the free form of the drug (Salem & Düzgünes, 2003; Labana *et al.*, 2002). Other studies showed lowered toxicity to surrounding tissues (Deol & Khuller, 1997). This lowered toxicity is especially important in drugs that are in

themselves very toxic, like the drugs that are currently available to treat *Trypanosoma brucei* and *Trypanosoma cruzi*. Even though the *in vivo* effect against the parasite is not significantly better than the free drug, the liposomes did have a protective effect against the toxicity of the drugs used in certain instances (Papagiannaros *et al.*, 2005).

The objective of encapsulating antimalarials in liposomes is to minimise adverse effects, giving sustained release and protecting the drug from being broken down (Date *et al.*, 2007). In a study done by Bayomi *et al.* (1998), the maximum plasma concentration was increased in a shorter time for arteether encapsulated in liposomes. The time taken for the drug concentration to reach its maximum level was also shortened. In other words, more of the drug was available in a shorter time, when compared to an oral suspension. The arteether's bioavailability was close to 98% when formulated in liposomes, compared to arteether in suspension with a bioavailability of nearly 32% (Bayomi *et al.*, 1998). Other antimalarials that have been entrapped in liposomes before include, chloroquine and primaquine. Studies with chloroquine revealed chloroquine liposomes to be relatively stable and ready to be taken into the next phase of testing (Qui *et al.*, 2008). It becomes quite clear that liposomes can become a great asset in the battle against malaria.

#### **2.4.4. Enhanced activity of drugs against extracellular pathogens**

Liposomes most often increase the pharmacokinetics of drug, thus, doses remain within the therapeutic range longer, and specificity to a target increases the efficacy of the drug, while decreasing toxicity. Liposomes have been proven to be able to overcome bacterial resistance in some cases (Omri & Ravaoarino, 1996). Other studies even claim lowering the required dose necessary for effective treatment by between 4-16 times against *Pseudomonas* (Drulis-Kawa *et al.*, 2006).

#### **2.5. Disadvantages of Liposomes**

No drug delivery system is faultless; this is the case with liposomes as well. As liposomes are used to enhance and to increase the efficacy of a drug, the cost as well as all the other implications thereof must be taken into account. Cost is an issue when it comes to lipid drug delivery systems, as these systems are quite expensive to produce. The cost is high because of high costs associated with the raw materials used in lipid excipients as well as expensive equipment needed to increase manufacturing (Jeong *et al.*, 2007).

In most cases liposomal formulations are non toxic, but certain formulations such as the cationic formulations tend to be cytotoxic. This is especially true when liposomal doses are very high (Blomme, 2008). Other problems are the following:

### **2.5.1. Sterilisation**

The sterilisation of liposomes is a complicated conundrum, as liposomes are sensitive to high temperatures, as well as certain methods of radiation. Sterilising with chemicals is not a viable option either, as it may affect the stability of the liposomes. The only method for creating sterile liposomes is by filtering the liposomes through a 0.22  $\mu\text{m}$  membrane filter after production. This method is only suitable if the liposomes are smaller than 0.2  $\mu\text{m}$  in diameter. This method does not remove viruses (Sharma & Sharma, 1997). Another option is filtering the initial solutions through 0.45  $\mu\text{m}$  regenerated cellulose filters and glass fibre filters before starting production, thereafter the entire production process must be done under aseptic conditions (New, 1990).

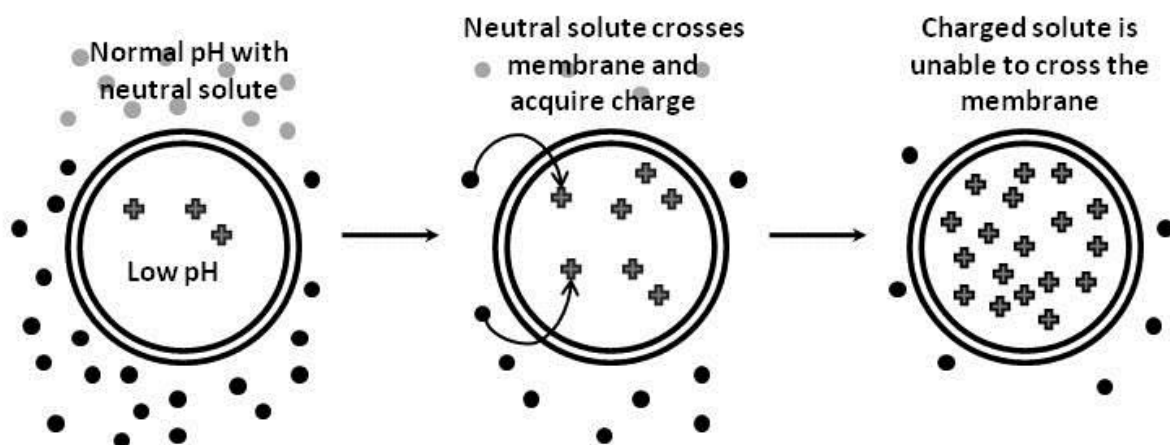
### **2.5.2. Short shelf life and stability**

For a pharmaceutical product to be viable for the market, it requires the product to be stable in some form or another for at least a year and a half to two years. To achieve this with liposomes is very difficult if the liposomes remain in suspension. Other methods may be used to increase the shelf life of liposomes, such as freeze-drying after production. Two factors play a major role in the stability of liposomes namely, chemical and physical degradation. The chemical degradation of liposomes is attributed to oxidation and hydrolysis. To decrease oxidation and hydrolysis, use only fresh and new reagents of the highest quality (Storm & Crommelin, 1998), avoid methods that have high temperatures, use inert atmosphere to store liposomes, deoxygenate aqueous solutions and do all manufacturing in the absence of oxygen. Lastly an anti-oxidant such as  $\alpha$ -tocopherol may be added (New, 1990). Physical degradation is most often attributed to the difference in the packing density of the lipids in the bilayer structure. This can be fixed by incubating the liposomes at a temperature close to the phase transition temperature, until the arrangement of the lipids equalises. Fusion between liposomes is quite common; this type of instability is curbed by adding cholesterol into the lipid mixture to raise the  $T_C$  of the lipids. Different types of liposomes all have different issues when the composition of the membrane is changed. This is exploited in the creation of thermosensitive liposomes. The liposomes release the drug as soon as the temperature is high enough (New, 1990). Physical degradation is also a huge factor when formulations are freeze-dried. When products are

freeze-dried a so called cryoprotector must be added to ensure the product is stable when reconstituted (Sharma & Sharma, 1997).

### 2.5.3. Encapsulation efficacy

The amount of drug the liposomes can entrap is often very low. The drug must be able to entrap inside the liposome in a therapeutic dose. Otherwise the amount of lipids and or other constituents of the liposomes can become toxic; the pharmacokinetics of liposomal drugs can even be negatively affected. Therefore, the method of entrapment is of utmost importance. When entrapment of the drug is especially low, methods like active loading can be used to improve the entrapment. This method involves using an uncharged drug that can easily cross the lipid bilayer in uncharged form, but changes to the charged species once inside the liposome. The drug is then unable to escape the interior of the liposome in the charged form. The effect can be created by entrapping a low pH environment inside the liposome and suspending the vesicles in a neutral pH environment, which contains the drug (New, 1990; Qui *et al.*, 2008). A simplified version of this is explained in Figure 2.6.



**Figure 2.6: A simplified illustration of the active loading of Liposomes, as adapted from New, 1990.**

### 2.5.4. Removal from circulation by the Reticulo-endothelial system (RES)

One of the major draw backs of liposomes as a drug delivery system is the rapid clearance from the blood stream by phagocytic cells of the mononuclear phagocyte system (MPS), which is also referred to as the reticulo-endothelial system (RES). The speed by which uptake takes place is dependent on a few factors, including the size and charge of the liposomes. Larger liposomes are eliminated from circulation faster than smaller liposomes (Gregoriadis, 1995). The liposomes accumulate in the liver and the spleen, because of the rich blood supply as well

as the amount of macrophages that accumulate there (Storm & Crommelin, 1998). Some strategies to prolong circulating time have come to light, such as the formulation of long-circulating liposomes or so called LCL's. These liposomes are formulated in different ways, such as coating the liposome with a polymer, with the most popular one being; coating existing liposomes with polyethylene glycol (PEG). These liposomes are often referred to as "stealth" liposomes (Deol & Khuller, 1997; Pinto-Alphandary *et al.*, 2000). Another alternative is including cholesterol and sphinomyelin (SM) in the formulation to increase the  $T_C$  of the formulation. This increases the stability of the liposomes in plasma and reduces the uptake by the RES (Betageri *et al.*, 1993).

## 2.6. Interactions of liposomes with cells

The interactions of liposomes with cells are important as this behaviour can often help predict why liposomes react in certain ways *in vitro* as well as *in vivo*. The ways in which the liposomes interact with cells are as follow:

### 2.6.1. Intermembrane transfer

This type of interaction occurs when the lipid components of liposomes interact with cell membranes. The components such as the PC, cholesterol and PE can exchange freely from one membrane to the other without disrupting the liposome integrity. This interaction may not even disturb the liposome's aqueous interior (New, 1990). This is an approach often used for cells that are not actively phagocytic. The membrane components play a large role in the interactions of this type (Betageri *et al.*, 1993).

### 2.6.2. Contact release

The precise way this interaction functions is not completely understood. When the liposome comes into the close proximity of cells, the interaction starts and the permeability of the liposomal membrane increases drastically. The increased permeability leads to the release of the aqueous interior, or in other words, the liposome's content. This causes a very high dosage of the drug in the cells vicinity. The effect seems to be more pronounced in liposomes that have a cholesterol concentration above 30 mol % (Van Renswoude & Hoekstra, 1981).

### 2.6.3. Adsorption

Cell adsorption occurs when the liposome attaches to the surface of a cell. The content of the liposome is not necessarily released into the cell, neither the lipid nor aqueous components. This is attributed to attraction between the membranes. Specific surface receptors are thought to play a role in this interaction. This interaction is very important as it is the first step that has to take place before pinocytosis or phagocytosis can occur. However, the factors involved are not fully understood (Betageri *et al.*, 1993).

### 2.6.4. Fusion

This type of interaction is quite rare, even though it was once thought to be the main method of interaction. The liposomes come into close proximity of the cells, from where the fusion can then take place. The liposome content is completely introduced into the cytoplasm of the cell. So called fusogens can be used to help this type of interaction, but these chemicals are often the cause of toxic effects, as they disturb the cell membrane even after the interaction has been completed. Fusogens include lysolecithin, surfactants and detergents (Betageri *et al.*, 1993). This method does not normally occur very often, because phagocytosis takes place faster and liposomes are thus rapidly removed from circulation by the RES (New, 1990).

### 2.6.5. Phagocytosis or endocytosis

Cells that have a phagocytic ability like the cells of the RES invaginate the liposome through the cell membrane and into a sub-cellular vacuole. Lysosomes then attach to this internalised vacuole which contains the liposome. The lysosomes introduce lysosomal enzymes that break down the lipids of the liposomes to fatty acids and in so doing, release the solutes contained in the liposome. The solute can slowly leak into the cell if the solute is not highly charged at a low pH (Betageri *et al.*, 1993). Endocytosis can also occur, which then gives the liposomes access to other cell organelles like the Golgi apparatus. This interaction is dependent on the interactions the liposome have with the surface receptors of the cell. If transferrin is added to the outer surface of the liposome, the liposomes activate cell receptors that cause endocytosis instead of phagocytosis to take place (New, 1990).

## 2.7. Commercial products containing liposomes

The products on the market which contain liposomes are few and far between, but this drug delivery system is proving its worth when applied in the real world. Broadly, there are two separate classes of drugs that contain liposomes for treatment in humans, these classes being fungus infections and cancer (Storm & Crommelin, 1998).

Currently amphotericin B is used with great success in severe fungal infections. Amphotericin is notoriously difficult to give parenterally because of the low tolerability, but liposome formulations have decreased the toxicity (Van Etten *et al.*, 1995), which made it possible to considerably increase the dose as the therapeutic index was improved. This gave an increase in overall efficacy. Three different liposome-amphotericin products currently on the market, Abelcet™, AmBisome™ and Amphocil™ have completely different morphological and formulation setups, but still give this improvement (Hillery, 1997).

When applied to anticancer therapy, liposomes were found to be very effective because of the specific targeting to cancer cells that is possible to achieve with targeted liposome systems. The liposomal formulations known as Doxil™ and DuanoXome™ are on the market, with research being done to expand the scope for these systems. These liposomes are specific to tumours, and therefore, toxicity is reduced (Storm & Crommelin, 1998).

## 2.8. Conclusion

Since the discovery of liposomes in 1964, the field and applications thereof has broadened considerably. Liposomes may be composed of a whole host of different lipids, manmade or naturally occurring, each having their own uses, advantages and disadvantages. The most used lipid component is phosphatidyl choline, because of its tendency to be neutral and relative low in cost. Another component usually added to the lipid mixture is cholesterol as cholesterol provides added stability. Liposomes can be classified according to production method, composition as well as size and shape. The advantages of using lipids as a drug delivery system include: decreased toxicity, improved pharmacokinetics and pharmacodynamics, enhanced efficacy against pathogens and programmable target selectivity. The disadvantages on the other hand are: certain lipids, especially charged lipids, become toxic in increased doses, sterilisation is a huge obstacle, problems with short shelf-life and stability, and problems with encapsulation efficacy. The interactions of liposomes with cells are very important as they influence how the drug is delivered. Liposomes have been in use as drug delivery systems for a few years with a few formulations commercially available, which show great affectivity. Liposomes have great promise as a drug delivery system.