designs for health® Australia

# LIPOCELLE™ TECHNOLOGY

## Designs for Health Lipocelle™ Technology is a visionary new development for the Australian practitioner market.

Australian made, using an ultra-high sonication process producing smaller particle sizes for therapeutic efficacy and results you can rely on.

TGA Listed

Soy-Free

Gluten-Free

GMO-Free

Dairy-Free

Liposomal Delivery

Australian Made

## OVERVIEW

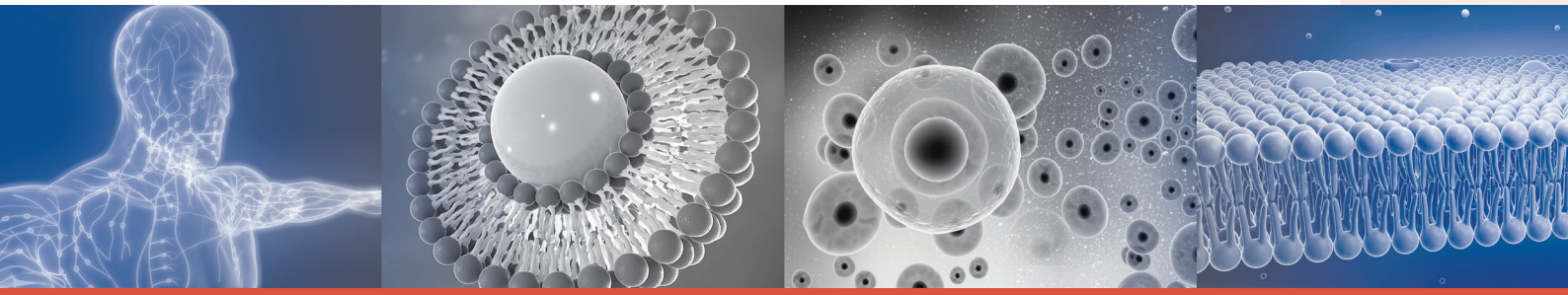
> Innovative and exciting new development for the Australian manufacturing industry
> Manufactured in an advanced licensed TGA facility to strict GMP standards ensuring high quality raw materials and finished goods
> Ultra-high sonication process produces smaller particle sizes (from 40-100 nm) Particle size has a significant impact on pharmacokinetic and pharmacodynamic properties and therefore therapeutic efficacy[6]
> Gluten-free, dairy-free, GMO-free and soy-free

## ADVANTAGES OF USING LIPOSOMES OVER TRADITIONAL DOSAGE FORMS

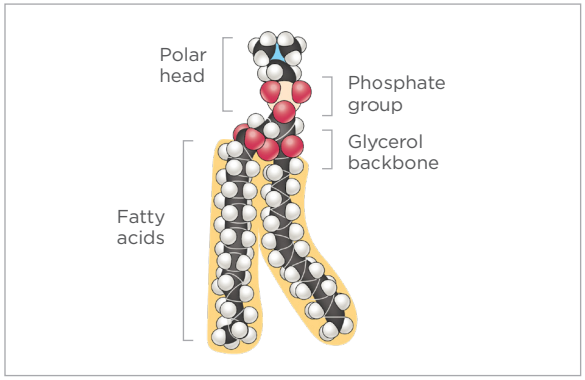
- ✓ Increases absorption/bioavailability and cellular uptake[3,5,6]
- ✓ Biocompatible and biodegradable due to likeness to biomembranes[1,5,8]
- ✓ Medicine is protected from degradation until it reaches target site[5,6]
- ✓ Facilitates targeted cellular delivery[5]
- ✓ Minimal toxicity as the medicine does not accumulate in non-targeted tissues, and resembles biological tissues[7,8]
- ✓ Dosing can be tailored more specifically
- ✓ Better compliance for patients who struggle with taking large tableted or capsulised medicine forms

### What is a Liposome?

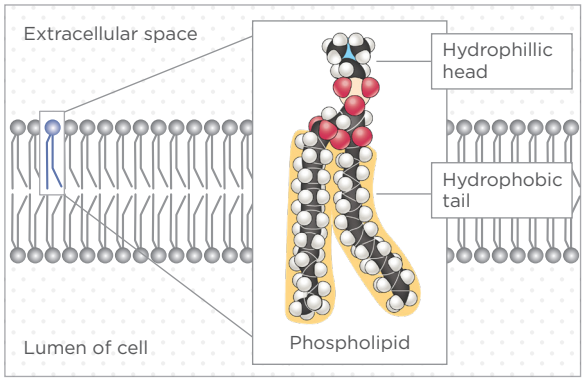
Phospholipids are a naturally occurring class of lipid molecule made up of a phosphate head, a glycerol backbone and two fatty acid tails. They are amphipathic – both hydrophilic and hydrophobic (the phosphate head being polar – electrically charged and hydrophilic; and the fatty acid tail being non-polar – neutral, hydrophobic and water-insoluble).[1,4] Phospholipids can arrange themselves as a "double layered" structure in an "upside-down" presentation with the phosphate (polar) head pointing outwards on both surfaces (enabling it to interact with aqueous solutions) and the non-polar tails facing inwards towards each other. When organised in this way, phospholipids form the structural basis of human cell membranes.[4] Cell membranes are almost impenetrable to most polar (hydrophilic) molecules.[4]

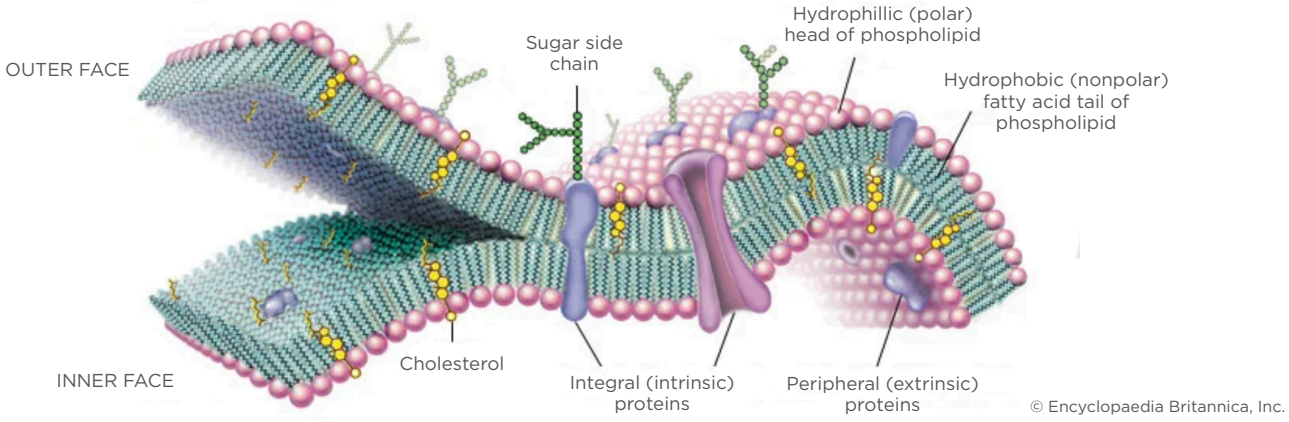


### A phospholipid molecule




### Lipid Bilayer Arrangement




### The Cell Membrane

In the early-mid 1960's, Alec Bangham discovered that when phospholipids are added to water-based solutions, they can form artificial protective spherical structures called liposomes.[2,4,5]

Liposomes have since been defined as "spherical vesicles with particle sizes ranging from 30nm to several micrometres"[1], and "phospholipid vesicles consisting of one or more concentric lipid bilayers enclosing discrete aqueous spaces".[3]

Liposomes are classified according to size and how many bilayered membranes exist (unilamellar or multilamellar). Liposomes intended for oral use can be classified as large unilamellar vesicles (LUVs) that measure ≥ 100nm, small unilamellar vesicles (SUVs) measuring 20-100nm, and multilamellar vesicles (MLVs) which measure ≥500nm.[7,8,9]

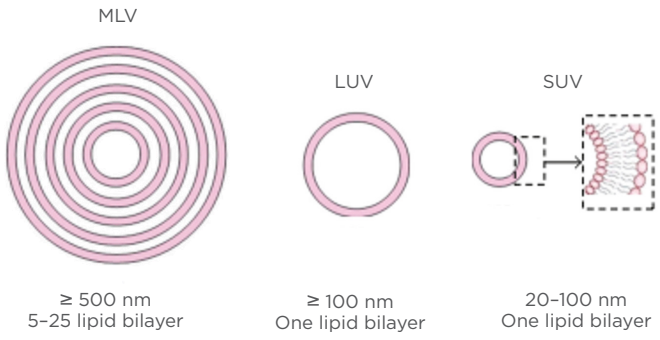
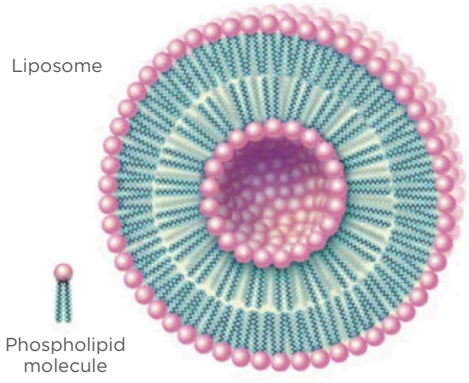



**Figure 1:** Classification of liposomes and their relative sizes. SUV: single unilamellar vesicles, MLV: multilamellar vesicles, LUV: large unilamellar vesicles.

## HOW DO LIPOSOMES IMPROVE MEDICINE ABSORPTION?

- ✓ Liposomal engineering increases the likelihood of lymphatic transport which avoids first-pass hepatic metabolism improving bioavailability, drug concentration and stability.[3,6]
- ✓ Phospholipid outer shell mimics cellular physiology which improves cellar uptake and facilitates targeted cellular delivery.[3,5]






## A Liposome

Being made up almost entirely of phospholipids, and therefore having the ability to mimic the physiology of a cell membrane with its biocompatible outer lipid laminate, liposomal technology can be harnessed to facilitate targeted medicine delivery directly into cells. This technology has been broadly adopted by both the pharmaceutical and complementary medicines industries as it improves pharmacokinetics and biological dissemination of the enclosed therapeutic compound, whilst reducing its toxicity.[3,8]

When engineered as a medicine delivery system, the liposomal vesicle is used as a hollow protective enclosure to encapsulate or enmesh a therapeutic compound.[1,2,4] This protective barrier prevents the embedded medicine from enzymatic and digestive degradation (in the mouth and stomach) and oxidative damage, thus maintaining its integrity. The outcome is that the medicinal compound remains undamaged and unchanged until it is delivered to the cell where it is offloaded and utilised.[1,3,6]

Being amphipathic, liposomes can affix both lipophilic and hydrophilic therapeutic compounds. Lipophilic particles are enmeshed in the fatty acid tails or non-polar area of the bilayer, and hydrophilic molecules are enclosed inside the aqueous nucleus of the phospholipid sphere.[3,6]

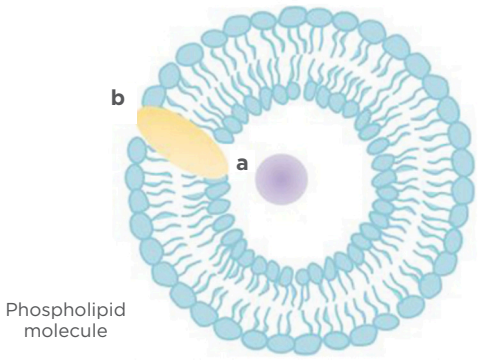



**Figure 2:** Liposomes with a hydrophilic drug **a** encapsulated in the aqueous core and a hydrophobic drug **b** incorporated into the membrane.

Therefore, medicinal compounds that have traditionally been difficult to employ due to rapid degradation upon exposure to digestive secretions and pro-oxidants, as well as hydrophilic therapeutic compounds which struggle to penetrate the cell membrane without a carrier, can be administered effectively in liposomal form.[2,3]

## Pharmacokinetics

Delivering therapeutic substances in such a way that maintains optimal bioavailability, concentration and stability whilst reducing the risk of toxicity has traditionally been challenging.

After a medicine has been administered orally, it is transported through the small intestine and can be taken up either by the portal vein or the intestinal lymphatic system. Water soluble medicines often enter the portal vein where they are transported to the liver and metabolised. This lowers the concentration of the substance and makes it less bioavailable. Uptake by the intestinal lymphatic system avoids first-pass hepatic metabolism, so concentration and bioavailability are maintained.[6]

Lipophilic medicines are preferentially taken up by the intestinal lymphatic system, so manipulating both hydrophilic and lipophilic therapeutic compounds to display the characteristics of lipids (as is the case with liposomes), increases lipophilicity and routes these medicines towards intestinal lymphatic transport systems.[6]

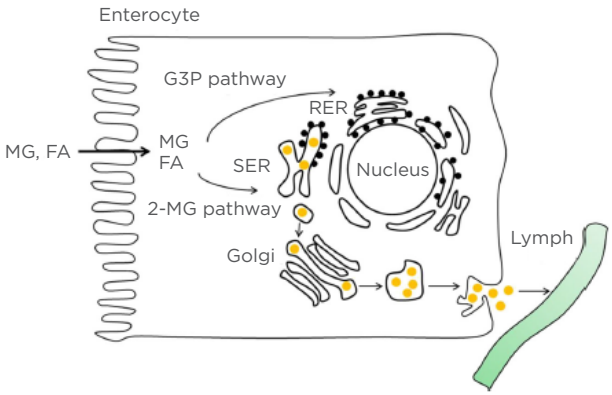



**Figure 3:** Pathways of lipid absorption and chylomicron synthesis within enterocytes.

Lipid molecules are absorbed by enterocytes where they are modified to chylomicrons and released into lymphatic vessels. Chylomicron production takes place in the endoplasmic reticulum (ER) and begins when monoglycerides and fatty acids are converted to triglycerides (TGs) by one of two pathways – the α-glyerol-3 phosphate pathways in the rough ER, and the 2-monoglyceride pathway in the smooth ER. Chylomicrons are synthesised from the resulting TGs in the ER.

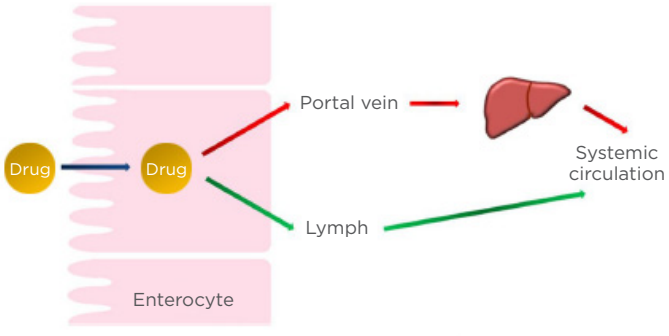



**Figure 4:** Two pathways (portal vein versus lymph) of oral drug transport to systemic circulation.

The chylomicrons are then transferred to the Golgi apparatus and secreted from the enterocyte into lymphatic circulation.[6]

There are also valuable absorption sites in the Peyer's patches of the intestinal mucosa which have been shown to contribute to total oral absorption. M cells which reside in Peyer's patches are accessible for liposomal absorption by mechanisms such as fluid phase endocytosis, adsorptive endocytosis and phagocytosis. Via these mechanisms liposomal medications are also able to enter lymphatic circulation, once again, bypassing hepatic metabolism.[8]

Smaller liposomal size ensures higher enterocyte uptake[6] and increased blood circulation time.[7]

### Buccal and Sublingual Absorption

The mucosa of the oral cavity including the papillae of the tongue provides an extremely large surface area for medicine absorption. The oral mucosa contains a prolific amount of blood vessels arranged in large and dense loops running parallel or vertical to the epithelial surface depending on their anatomical location (i.e., the gingiva or the tongue respectively). The oral floor contains dense networks of blood capillaries as does the back of the tongue, the gingiva and the oral vestibule.[12]

Substance breakdown and assimilation is one of the major functions of the oral mucosa. Compounds of low molecular weight are able to be absorbed into the blood vessels via the oral epithelial tissues.[12]

The density and arrangement of the oral blood vessel network is vital for medicine absorption. Areas where blood vessel arrangement lies parallel to the basal membrane such as the non-keratinised vestibulum oris and oral floor, offer a great area of contact with the epithelium, facilitating nutrient transfer, whereas, the existence of papillae on the tongue allows for blood vessel looping, increasing the density of the entire capillary network.[12]

The membranes of the oral floor (sublingual area) provide the most permeable area of the mouth, followed by the buccal (inner cheek) area. Permeability is determined by the degree of keratinisation and vascularity, as well as the thickness of the epithelial tissue.[11] The degree of medicine lipophilicity is also a strong determinant for sublingual and buccal absorption. Medicines with high lipid solubility (such as liposomes) are more likely to be absorbed than their water-soluble counterparts.[11]

Medicine absorption via the mucous membranes in the oral cavity occurs via passive diffusion into the lipoidal tissue, and can occur 3-10 times faster than swallowing a tabletted or capsulised therapeutic compound, whilst also bypassing first-pass hepatic metabolism.[11,12] The medicine is absorbed into the reticulated vein underneath the tongue. It then travels through the facial veins, the internal jugular vein and the brachiocephalic vein before finally before finally entering the systemic circulation.[11]

*References supplied on request.*

## MANUFACTURING PROCESS

1. Ethanol soluble ingredients are weighed
2. Ethanol soluble ingredients are mixed with ethanol
3. Water soluble ingredients are weighed
4. Water soluble ingredients are mixed with water
5. Ethanol and water solutions, from above, are mixed together
6. Ultra-high sonication with a sonotrode to reduce particle size and create liposomes