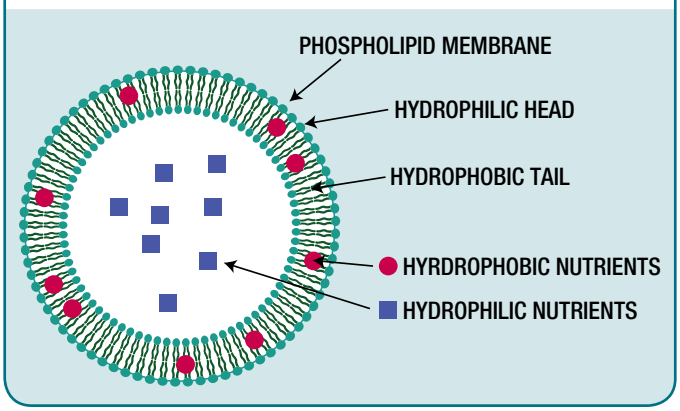
Liposomes

Liposomes are spherical vesicles consisting of one or more phospholipid bilayers.[1] Discovered in the early 1960s by British biophysicist Alec Bangham, liposomes were first used as artificial membrane models, mimicking simple cell systems for the investigation of transport functions, mechanisms, permeation properties as well as adhesion and fusion kinetics.[1] However it wasn't long after their discovery that liposomes were recognised as promising systems for drug delivery.[1,2]

FIGURE 1. Cross section of a liposome.[3]



Liposomes are constructed of polar lipids which are characterised by having a hydrophobic and hydrophilic group on the same molecule.[3] Upon interaction with water, polar lipids self-assemble and form colloidal particles where ultramicroscopic particles of one substance are dispersed through another substance.[3.] As depicted in figure 1 the hydrophilic head of the phospholipid orients towards the water compartment and the hydrophobic tail orients away from the water into the centre of the vesicle, forming bilayers.[4]

The unique structure of liposomes provides the ability to entrap both water soluble molecules (such as vitamin C and vitamin B12) in their interior core, and fat soluble molecules (such as curcumin and coenzyme Q10) inside the hydrophobic bilayers; making them a popular delivery system in the pharmaceutical and nutraceutical industries.[4]

The characteristics of liposomes change the pharmacokinetics of the encapsulated active ingredient, improving the solubility, bioavailability and *in vitro* and *in vivo* stability.[4,5]

PEG-free Liposomes

Some liposome products contain the chemical polyethylene glycol (PEG), however by utilising a specialised combination of phospholipids and phosphatidylcholine, a stable liposomal matrix can be ensured without the use of chemicals such as PEG. PEG is a synthetic resin made by polymerising ethylene glycol, and is used industrially as part of adhesives, inks, paints and coatings, lubricants, anti-static agents, and also as part of a compound for plasticisers.[6] As PEG is a widely used chemical across multiple industries, regular exposure can occur through the use of products including deodorants, toothpaste, shampoo and moisturisers.[7]

PEG is also present in many medications administered by parenteral, topical, ophthalmic, oral and rectal routes.[7] In the pharmaceutical industry, the addition of PEG polymer chains to a drug, vesicle, protein, peptide or other molecule, is primarily used to improve pharmacokinetic properties, by reducing the clearance and increasing the half-life.[7]

As urinary clearance is the major excretion pathway for PEG, if toxicity is observed it is most frequently associated with the kidneys.[7] It is thought that PEG polymers of all molecular weights are excreted unchanged in the urine, however the rate at which this occurs is largely dependent on molecular weight; the larger the PEG polymer the longer the residence time in the body.[7] Therefore it is possible that larger molecular weight PEGs are more acutely toxic due to slow renal clearance, and have the potential to accumulate in the liver.[8]

There are also a number of recent reports raising concern over the immunogenicity and antigenicity of PEGs with a subset of individuals presenting with antibodies against PEG (anti-PEG). These anti-PEGs cause rapid blood clearance of the PEGylated molecule leading to limited therapeutic efficacy.[9,10] Further research is needed in this area.

BioMedica's Pure Liposome® formulas are made utilising world-class liposomal technology, which enables uniform micronized liposome vesicles that support increased circulation time and reduced clearance, thereby eliminating any need for PEG polymers.

ADVANTAGES OF LIPOSOMAL DELIVERY SYSTEMS:

- Supports the bioavailability of therapeutic substances via enhanced aqueous solubility.[4,11]
- Ability to encapsulate both water and fat soluble active ingredients.[4]
- Protection for sensitive active substances from degradation in the gastrointestinal tract.[4,11]
- Reduction of gastrointestinal side effects.[11]
- Composed of natural lipids which have important advantages by being biocompatible with human tissues; biologically inert, weakly immunogenic, and of limited intrinsic toxicity.[12]
- Oral liposomal liquids allow for flexible dosing and can be compounded for individualised prescribing.

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MECHANISMS OF ABSORPTION:

The mechanisms involved in the oral absorption of liposomes are not yet fully understood, however there are several suppositions. One proposed mechanism is the uptake of whole liposomes by M cells on Peyer's patches, see figure 2.[4,13] Liposomes have a similar structure to the biological cell membrane. This understanding has led to another theory which involves the fusion of the liposome lipid bilayer to the intestinal plasma cell membrane.[3] This then facilitates the release of the entrapped active into the cytoplasm as depicted in figure 3.[3]

Another proposed mechanism of absorption is through intestinal lymphatic delivery.[14] Micronized liposomes are said to transit across the enterocyte and associate with enterocyte lipoproteins to form chylomicrons that enter the lymphatic system, see figure 4.[14]

FIGURE 2. Proposed pathway of liposome absorption via intestinal epithelial uptake by M cells on Peyer's patches.[4,13]

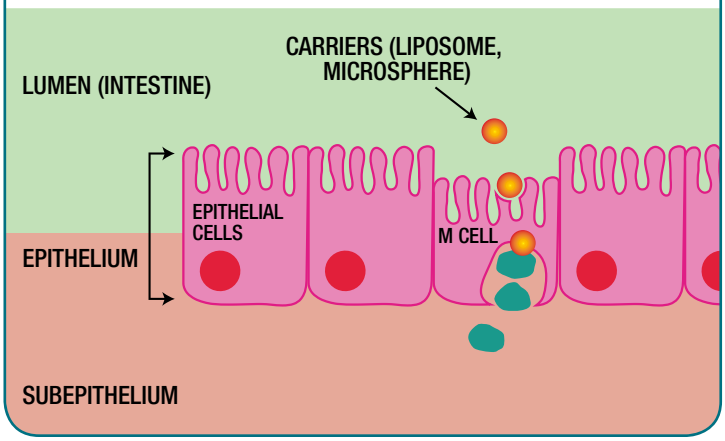


FIGURE 3. Proposed delivery of a liposomal encapsulated therapeutic substance into a cell.[3,15]

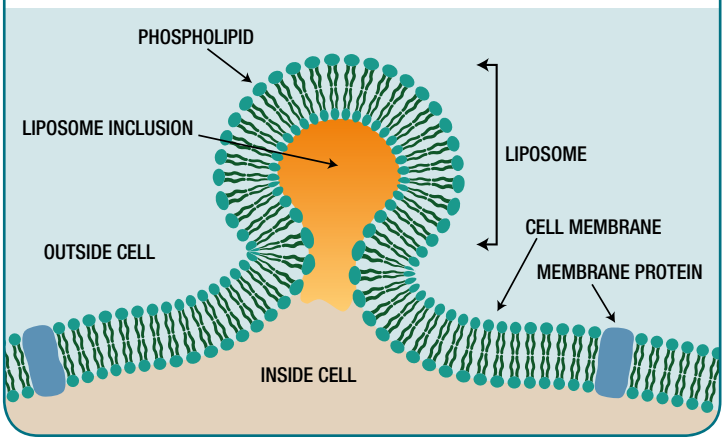
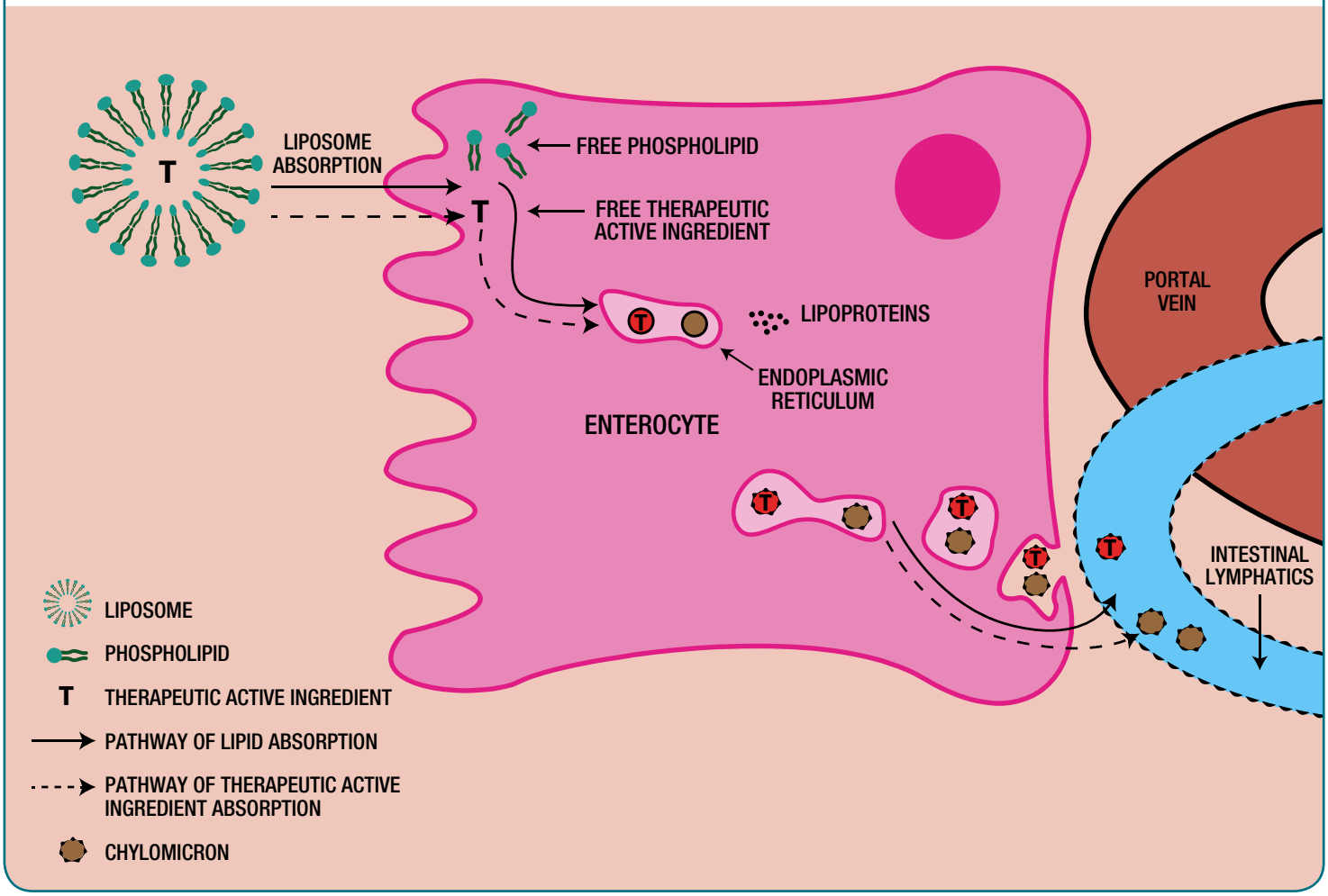


FIGURE 4. Proposed mechanism of liposome absorption via intestinal lymphatic delivery.



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CLINICAL CONSIDERATIONS:

Advanced liposome technology provides practitioners with an additional and alternative clinical prescribing option. There are numerous clinical presentations for which liposome formulas are well indicated; including chronic conditions where intestinal absorption may be compromised.

Liquid liposome dosage forms also offer a more suitable and compliance-encouraging option for patient populations who may not be well suited to tablet and capsule dosing forms, such as children, the elderly and those with difficulty swallowing large tablets or capsules.

Furthermore, high-quality and pure liposomes are formulated to provide effective doses of therapeutics without the use of chemicals such as PEGs, artificial colours or artificial flavours, or the binders and fillers found in some tablets.

Liposomal Therapeutic Delivery System Indications:

- **Patients with sensitive gastrointestinal tracts**
- **Elderly patients**
- **Children**
- **Inflammatory bowel disease**
- **Patients with dysphagia**
- **Those requiring high therapeutic doses**

CHOOSING A SUPERIOR LIPOSOME PRODUCT:

- A stable liposomal matrix – an individualised and unique combination of both phosphatidylcholine and phospholipids is required for each particular active being encapsulated, to ensure a stable liposome without the use of synthetic chemicals such as PEGs.[15]
- Uniform micronized particle – the vesicle size is an acute parameter in determining the circulation half-life of liposomes.[16] Small unilamellar vesicle (SUV) particles below 100nm support increased circulation time and therefore greater therapeutic potential.[16] Size is also one of the main parameters which determines the fraction cleared by the reticuloendothelial system (RES). Small liposomes (≤100nm) are opsonized less rapidly and to a lower extent, resulting in increased circulation time.[16]
- Free from polyethylene glycol (PEG)
- The use of high quality phospholipids and phosphatidylcholine from non-GMO sources
- High-quality active raw materials
- Bioavailability studies
- Proven stability data

BIOAVAILABILITY:

Figure 5. Plasma vitamin C levels plateau and only show minimal increases following standard vitamin C oral doses over 400mg/day.[18]

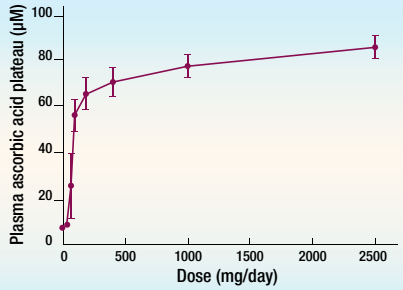
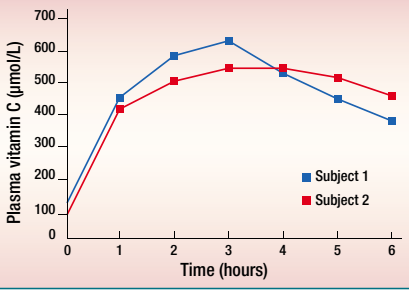


Figure 6. Plasma vitamin C levels increase without plateauing following administration of Pure Liposome® vitamin C.[15]



It is well known amongst health professionals that fractional absorption of oral vitamin C decreases with increasing intake.[17] Oral vitamin C administration is limited by saturation of intestinal absorption and osmotic diarrhoea with maximum tolerable oral doses in the range of 3-4g.[18]

Depletion-repletion pharmacokinetic studies have shown that, as a result of increasing oral vitamin C intake, plasma vitamin C concentrations rise steeply at doses under 100mg/day.[18] Oral vitamin C intakes between 100-400mg/day, results in a progressive flattening of the curve until plasma vitamin C levels reach a plateau at 70-80µmol/L.[18] At doses over 400mg/day further increases in plasma vitamin C is minimal as shown in figure 5.[18,19]

Using world-class pharmaceutical liposome encapsulation technology, higher doses of oral vitamin C can be administered with minimal gastrointestinal side effects; and greater plasma vitamin C concentrations can be achieved. This is due to the fact that liposomes are proposed to bypass regular vitamin C absorption pathways.[3,4,13,14]

Liposomal vitamin C at a dose of 36g was shown to raise plasma vitamin C concentrations above 500µmol/L in two subjects tested, a level only generally achievable using invasive intravenous administration, see figure 6.[15]

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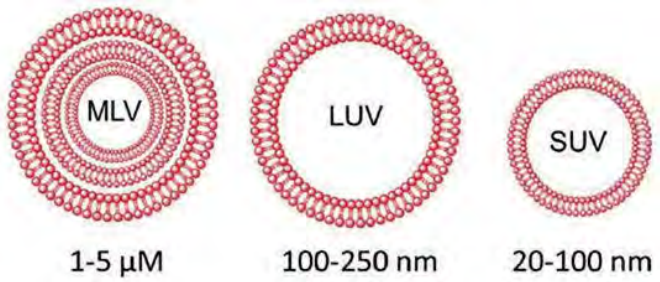
MICRONIZED LIPOSOMES

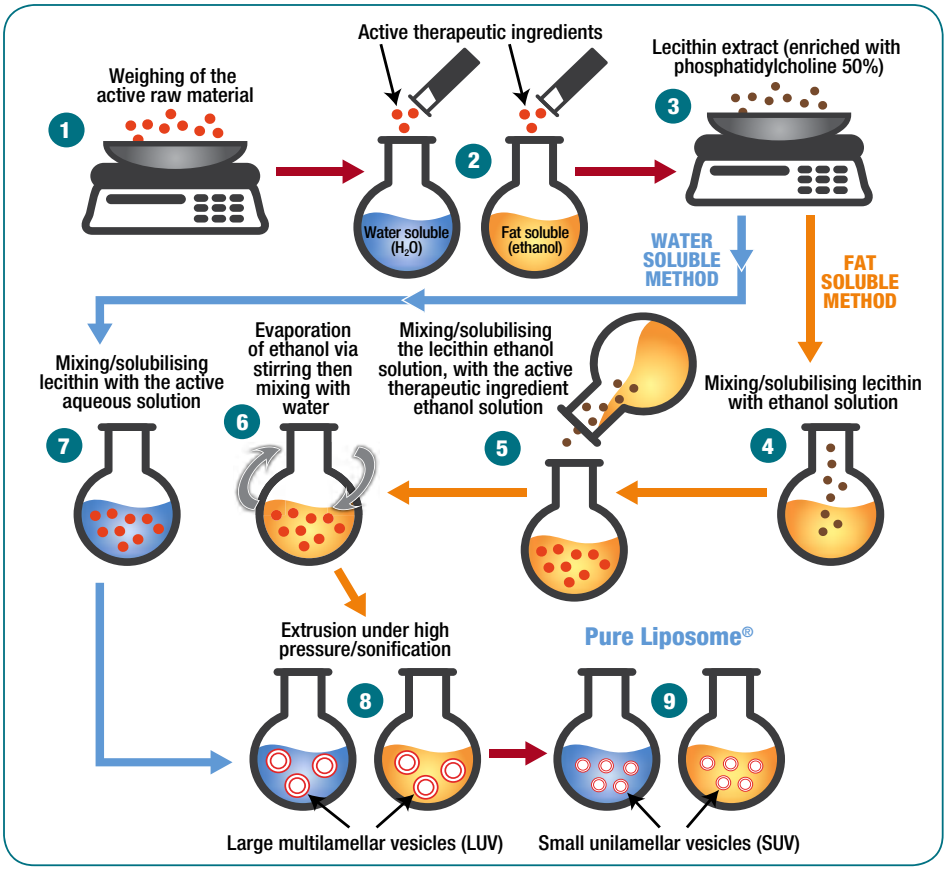
Figure 7. Types of liposomes depending on size and number of phospholipid bilayers.



Liposomes can vary in size and in the number of bilayer phospholipid membranes they contain, also known as lamellae. Based on size and number of bilayers, liposomes can also be classified as either multilamellar vesicles (MLV), large unilamellar vesicles, and small unilamellar vesicles (SUV). SUV particles below 100nm support increased circulation time and therefore greater therapeutic potential, see figure 7.

SUPERIOR LIPOSOME MANUFACTURING METHOD:[15]

1. Precise weighing of the active raw material
2. Solubilising the active ingredient in water (if water soluble) or ethanol (if fat soluble)
3. Precise weighing of the lecithin extract (enriched with phosphatidylcholine 50%)
4. Mixing/solubilising lecithin with an ethanol solution
5. Mixing/solubilising the lecithin ethanol solution, with the active therapeutic ingredient ethanol solution
6. Evaporate a large part of the ethanol under stirring (fat soluble active) then mixing the end product with water
7. Mixing/solubilising lecithin with the active aqueous solution
8. Extrusion under high pressure/ sonification – water soluble active and fat soluble active
9. Pure Liposome® (SUV)



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