50 nm and can be prepared on a large-scale by homogenization to disperse the lipid into an aqueous environment.

Solid lipid nanoparticle dispersions have been developed for parenteral, oral, ocular, dermal and cosmetic applications. As with the polymeric nanoparticles, PEG coating of these systems has been shown to passively target tumour sites via the EPR effect. To actively target cancer cells, covalent coupling of targeting groups such as ferritin or galactose to the lipids used in the formulation has been investigated. Currently, there are a range of cosmetic products which use lipid nanoparticles loaded with cosmetic components such as: ascorbyl palmitate, beta-carotene and co-enzyme Q10. As these are all lipophilic in nature, they are efficiently incorporated within lipid nanoparticles.

Protein nanoparticles

In addition to polymers and lipids, nanoparticles can also be prepared from proteins. The first commercial product based on protein nanotechnology was Abraxane® (nab™-paclitaxel). Abraxane® is approved for the treatment of breast cancer in patients who do not respond to combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Abraxane® consists of 130 nm particles of albumin-bound paclitaxel. The drug, paclitaxel, has a low water solubility and requires addition of solubility-enhancing agents to allow its clinical use. Prior to the development of Abraxane®, paclitaxel was only available as Taxol®. This is a liquid product with paclitaxel solubilized in polyethoxylated castor oil (Cremophor® EL) and ethanol. However, this formulation requires special infusion sets, prolonged infusion times and has toxicity issues associated with its use. By incorporating paclitaxel into albumin nanoparticles, the albumin functions to coat the paclitaxel and provide colloidal stabilization to the drug. This circumvents both the low solubility and the Cremophor®-associated side effects.

Targeting mechanisms of Abraxane®

The albumin within the nanoparticle-albumin technology used in Abraxane serves as more than a solubility enhancing agent: albumin also promotes active targeting of the paclitaxel to tumour cells. As highlighted above, drug targeting of nanoparticles to tumours may be enhanced as a result of the EPR effect; the dense and highly permeable endothelial microvascular structure of tumours (which is a result of angiogenesis) allows large macromolecules and nanoparticles to leak into the underlying tumour tissue. The impaired lymphatic drainage at the tumour site slows drainage of these nanoparticles and macromolecules from the tumour site, resulting in the particles becoming trapped.

In the case of Abraxane®, a second mechanism has also been associated with the targeting and uptake of the albumin nanoparticles to tumour sites. This is the *Albumin-activated (glycoprotein) gp60 pathway*. Within the body, albumin is able to transport hydrophobic molecules, such as vitamins, hormones and other plasma constituents, across the endothelial lining and out of the blood circulation. This is achieved by albumin binding to gp60 albumin receptors found on the surface of vasculature endothelial cells. These gp60 receptors are then responsible for the transport of albumin across blood vessel walls. The binding of albumin to the gp60 receptors, activates the membrane protein caveolin-1. The activation of caveolin-1 subsequently results in the internalization of the cell membrane and the formation of transcytotic vesicles (known as caveolae). These caveolae then transport their contents across the endothelial cell cytoplasm, and release their contents into the cell's interstitium. In the case of tumours, this transport system is thought to be upregulated. Therefore Abraxane® is able to exploit this albumin-activated gp60 transport mechanism to target the tumour site. After entering the systemic circulation, the albumin-bound paclitaxel can bind to the gp60 albumin receptors and be carried across the endothelial cells via transcytosis in the same way as albumin.

After crossing the endothelial lining, the drug must cross the tumour cell membrane and enter the tumour cells. Once the albumin-bound paclitaxel reaches the interstitium, the albumin may bind to an extracellular matrix glycoprotein known as SPARC (secreted protein acid and rich in cysteine) which is also over-expressed in tumour cells. This can trigger the release of the paclitaxel from the albumin, allowing the free drug to diffuse to the nucleus of tumour cells initiating cell death. Given that this mechanism of tumour targeting is an attribute of the albumin carrier system and not the drug, it is conceivable it may be applied to the delivery of other low solubility anti-cancer agents.