Development of Cholestosomes, a novel neutral-lipid based drug delivery vehicle, using the molecular modeling program SYBYL

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Many promising drugs never evolve into effective treatments due to poor bioavailability that could stem from poor solubility, poor specificity or steric effects. Drug delivery vehicles, such as liposomes, niosomes and nanoparticulate carriers, have been created to try and solve these problems but even these vehicles have their limitations. Liposomes commonly contain a charge, which can limit the array of drugs that can be encapsulated, the surfactants used in niosomes can lead to toxicity when administered in high doses and nanoparticulate carriers usually can load only certain bioactive molecules (such as DNA). These vehicles also may have to be coated with a polymer, such as polyethylene glycol (PEG), to increase their stealth properties. In the present study a novel vesicle called a cholestosome has been developed based on molecular modeling. Thermodynamic and crystallographic studies were used to develop models of the vesicle. Molecular modeling using the SYBYL program was able to predict the structure of the cholestosome with certain properties such as a cavity in the middle and a certain size (approximately 200nm) and shape (spherical). Using the modeling information, a preparative method was developed to create this delivery vesicle. These were characterized using electron microscopy (EM) and dynamic laser light scattering (DLLS). In proof of principle experiments, cholestosomes have been shown to deliver substances, *in vitro*, into living cells. Some advantages that cholestosomes have over other delivery vehicles is they are made from binary combinations of neutral lipids and therefore contain no net charge, have a wide range of pH stability, and are not toxic to cells. A predicted advantage that the cholestosomes have is that because of the neutral charge they can encapsulate a wide range of payloads in its cavity. Comparison of van der Waals surface models of a four fatty acid esterfied PEG units of a pegylated liposome and a cholestosome suggest that the cholestosome has surface properties very similar to that of the pegylated liposome. Current work includes attempts to encapsulate Tobramycin, an aminoglycoside that has poor bioavailability.