CONTROLLING THE RELEASE KINETICS OF PHARMACEUTICALS *IN VITRO* USING LIPID CUBIC GELS AND DISPERSIONS

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Background: Lipid cubic phase formulations have gained considerable interest as controlled delivery systems for a range of active pharmaceutical and biological agents on account of their desirable physiochemical properties, and ability to encapsulate both hydrophobic and hydrophilic molecules. Their formation is driven by a hydrophobic effect, whereby, under specific environmental conditions, the amphiphilic molecules spontaneously self-assemble in a bid to shield their hydrophobic moieties from an aqueous environment.

In vivo, the biodegradable formulations are susceptible to lipolysis by a variety of biological enzymes, including lipases and esterases, likely influencing the release of the actives from their network. In particular, the release of poorly soluble molecules residing in the lipid membrane portions of the phase is limited by the breakdown of the matrix; thus presenting a means for gaining further control and a more sustained release by targeting the matrix stability and its rate of degradation is desirable.

Methods: The aims of the present study were twofold: to evaluate an approach to regulate the rate of degradation of lipid cubic phase drug delivery systems by targeting the enzyme interactions responsible for their demise using a known potent lipase inhibitor; and to study the subsequent drug release profiles from bulk lipid cubic gels using model drugs of contrasting solubility by means of UV-vis spectroscopy and HPLC .

Small-angle X-ray scattering was utilized to study the effect, if any, of incorporating the inhibitor into the lipid membrane of the lipid cubic gels. Standard gravimetric approach was taken to track changes in mass of the gels owed to lipolytic hydrolysis by lipases as a means of quantifying their stability in soluion.

Results: Hybrid materials consisting of cubic phases with monoacylglycerol lipids of different chain lengths formulated with a potent lipase inhibitor tetrahydrolipstatin were designed. The structural properties of the novel inhibitor-cubic phase formulations were extensively studied using synchrotron SAXS and demonstrated no negative effect on the internal nanostructure of the phase. To demonstrate the inhibitor effect, modulation of the release of two model pharmaceuticals were studied. It was shown that the stability of the lipid gels in the presence of enzyme could be tuned from approximately 1 week to beyond 4 weeks by increasing the concentration of inhibitor loaded into the gel. Subsequently, the release of the hydrophobic agent could be controlled in this way simply by addressing the digestion of the lipid envelope.

Conclusions: We have demonstrated a novel working system for addressing the susceptibility of these lipid formulations to control the stability and subsequent delivery of hydrophobic molecules without negatively impacting the structure of the phase.

M. Dully, C. Brasnett, A. Djeghader, A. Seddon, J. Neilan, D. Murray, J. Butler, T.Soulimane, S.P. Hudson, Modulating the Release of Pharmaceuticals from Lipid Cubic Phases using a LipaseInhibitor, Journal of Colloid and Interface Science (2020), doi: https://doi.org/10.1016/j.jcis.2020.04.015.