Title	Triple HIV Drug Combination and Lipid Excipients Form Stable Solid State Interactions Leading to an Ordered Matrix for Enhanced Drug Delivery
Keywords (up to 5)	Drug delivery, HIV, Fixed Dose, Drug Combination, Lipid Excipients
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Abstract	Daily oral drug-combination therapy is the standard of care to provide sustained HIV viral suppression and mitigate drug resistance. Treatment regimens are formulated as fixed dose combinations that target multiple points in HIV viral replication[1]. Inhibitors for HIV reverse transcriptase (RT), integrase (InT) and protease (Pr) exhibit disparate physicochemical properties with RT inhibitors having high aqueous solubility and InT/Pr inhibitors having low aqueous solubility. Limited aqueous solubility of hydrophobic drug compounds pose challenges to producing fixed dose combinations with hydrophilic RT inhibitors. Spray drying of hydrophobic drugs is a process that can be considered to produce amorphous fixed dose combination products. However, amorphous products carry high energy states and are inherently unstable[2]. We have investigated whether HIV drug-combination with disparate degrees of water solubility can be stabilized by well-defined lipid excipients in the solid state through controlled solvent evaporation. Three antiretroviral drugs, lopinavir (LPV), ritonavir (RTV) and tenofovir (TFV) with distinct LogP values (4.7, 5.2, -3.6, respectively) were used for this study. Compounds were co-dissolved with lipid excipients and dried using an optimized spray drying process. The resulting powder was analyzed by powder X-ray diffraction (XRD) and differential scanning calorimetry (DSC). Relative to the admixed controls, loss of drug crystallinity is observed in the drug-combination powder product. Instead, two distinct peaks observed in XRD suggest a d-spacing of 4.1 Å and 15.4 Å. This result is corroborated by a single endotherm observed at 79.4°C in DSC. Drug distribution and particle morphology were evaluated by time of flight secondary ion mass spectroscopy and scanning electron microscopy. The drug-combination powder was homogeneous in both regards. Collectively, these data suggest that this drug-combination with lipid excipients forms a uniform and organized structure. This structure provides an ordered matrix in which both hydrophilic and hydrophobic compounds can be stabilized for enhanced drug delivery.
References	1. Maartens, G., et al. (2014). "HIV infection: epidemiology, pathogenesis, treatment, and prevention." Lancet 384(9939): 258-271. 2. Yu, L. (2001). "Amorphous pharmaceutical solids: preparation, characterization and stabilization." Adv Drug Deliv Rev **48**(1): 27-42.