Lipid based formulations can be used to control the solid state form of poorly-water soluble ionisable drugs upon precipitation during *in-vitro* digestion

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A common approach to increase the oral bioavailability of poorly water-soluble drugs is to use lipid-based formulations (LBFs). These formulations aim to maintain lipophilic drugs in solution throughout gastrointestinal transit, effectively transporting these drugs, via colloidal structures formed by digestion products, to sites of absorption in the small intestine. The reality, however, is that LBFs can lose their drug solubilisation capacity as lipid digestion proceeds. As lipids are digested, supersaturation of drug in the formulation and colloidal phases can occur, which can drive the precipitation of drug. The aim of this work was to establish the apparent link between the solid-state form of compounds with a range of physicochemical properties upon precipitation, during the digestion of LBFs, with the pKa of the compounds relative to the pH of the digesting medium, or their ionisation state. The weakly basic drug cinnarizine was shown to precipitate in a non-crystalline form when a model LBF was digested at a pH (6.5, 5.5 and 4.0) below the pKa of the drug (7.4), but precipitated crystalline when the LBF was digested at pH 8.0. A shift in the C-N IR-absorption band for precipitated cinnarizine at pH conditions below the pKa of the drug, supports an interaction between cinnarizine and oppositely-charged species (fatty acids) during digestion of the LBF, which caused cinnarizine to precipitate as an amorphous-salt form. Analogously, the weakly acidic drug tolfenamic acid was shown to precipitate as an amorphous-salt when oppositely-charged cationic surfactant (DDAB) was added to a model LBF at a 1:1 drug/surfactant mol ratio, but precipitated in a crystalline form when the same LBF without DDAB was digested. Improved dissolution properties of these amorphous-salt forms relative to crystalline forms may potentially allow for the re-dissolution of precipitated drug in the dynamic absorptive environment of the small intestine *in-vivo*. 