Mechanisms of increased bioavailability

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There are various physical, chemical, and biological mechanisms underlying the increased bioavailability of certain formulations. Firstly, encapsulation in emulsions, micelles, lipid particles, or liposomes provides physical protection to cargo molecules and may facilitate their passage through the stomach to absorption sites in the small intestine. The key physical mechanism which is shared by all formulations designed to increase oral bioavailability is maintaining cargo in a soluble state within the GI tract. Only molecules in the soluble state are accessible to enterocytes for absorption (bioaccessibility). Once within the small intestine, lipid-based preparations are partially digested (lipolysis) and the liberated molecules (free fatty acids, monoacylglycerols, and diacylglycerols) join with endogenous phospholipids and bile salts to form ‘complex missed micelles.’ Lipophilic bioactive cargo/supplement molecules are solubilised in these micelles and delivered to enterocytes where they are absorbed by both active and passive transport mechanisms. The process of complex mixed micelle formation and the resultant solubilisation of exogenous bioactive molecules is key to increasing the bioavailability of lipophilic molecules that the body would otherwise be unable to absorb. Compounds present within novel formulations, such as surfactants, may also directly interact with enterocytes and increase their permeability. This can occur through the opening of tight junctions with resultant increases in trans-

cellular transport. The expression and activities of transporter proteins may also be affected by lipidic excipients which may favour the absorption of specific bioactive molecules. Direct mechanisms of uptake may also be promoted by these formulations. For instance, liposomes may fuse directly with enterocyte membranes or be endocytosed and release their contents inside the cell. Moreover, bioactive molecules associated with lipid compounds may be intracellularly trafficked into chylomicrons with resultant export into the lymphatic system. This process may protect associated cargo from metabolism within enterocytes. Lymphatic absorption with paracellular and/or transcellular pathways and/or via M cells also occurs for lipid nanoparticles and emulsion droplets that have not been digested within the small intestine. Finally, some of these preparations exhibit particles existing at the nanoscale, which may impart unpredictable biological effects to both the active agent *per se* and its physical-chemical structure These mechanisms, which may overlap between different formulations have potential to later the bioavailability and downstream kinetics (distribution, metabolism, excretion) of bioactive molecules.