Physical-chemical properties of novel bioavailable supplement formulations

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20. Appendix A: Literature search for specific toxicology studies with novel supplement formulations

The oral bioavailability of bioactive molecules is related to their solubility. Only molecules of intermediate solubility (i.e., those that are readily solubilised within the aqueous environment of the gastrointestinal tract (GIT) and which pass readily through the nonpolar lipid bilayer of enterocytes) will be readily absorbed by the body. Hence, molecules that are either highly hydro- or lipophilic are of low intrinsic oral bioavailability. However, a large body of evidence demonstrates that altering the formulation of bioactive compounds (e.g., vitamins, minerals, plant metabolites) can influence their bioavailability and other physical and toxico/pharmacokinetic properties, including stability (inside and outside the body). Specifically, alterations in the particle size of active agents, addition of excipient compounds, and/or encapsulation or emulsification within lipid/oil phases have the potential to increase the rate and/or extent of that agent's absorption. Although many of the systems described above were initially developed by the pharmaceutical industry to modify the kinetics of pharmacotherapeutics, formulations with similar structural, physical, and chemical properties can be assembled using food-grade ingredients and are increasingly observed on the supplement market. Tuning the structural, physical, and chemical properties of these systems can result in different biological effects.

For highly lipophilic compounds the primary strategy that has been used to increase oral bioavailability is lipid/oil-based and amphipathic delivery systems. Most common among these are emulsions, micellar, and liposomal preparations. These systems function by increasing the aqueous solubility of lipophilic molecules. Emulsions, for instance, are colloidal liquids in which oil droplets are dispersed in water, forming a stabilised interfacial film of surfactant. Bioactive molecules, also referred to as 'cargo', dissolved in these oil droplets are maintained in a soluble state within an aqueous medium, which facilitates their bioavailability. There are several types of emulsions, including microemulsions, nanoemulsions, self-emulsifying systems, (solid) lipid nanoparticles, and nanostructured lipid carriers, which have different properties that may affect how they interact with biological systems. Unlike emulsions, liposomes and micelles are composed of amphipathic/surfactant molecules. In micelles, surfactant molecules self-assemble into spherical structures with the hydrophilic portion of the molecule facing outward when suspended in aqueous media. Liposomes are structured as a bilayer that have an aqueous interior. For both systems, active agents are dissolved either in the lipophilic or hydrophilic components of the surfactant structures as a function of their preferential solubility. Several non-

lipid-based formulations designed to increase oral bioavailability have also been reported in the literature, although these have been less frequently observed within the supplement market. Examples include the use of fibre and polysaccharides to complex lipophilic compounds and keep them solubilised in the GIT. Physical mechanisms including micronisation and nanoisation fragment particles of an active molecule into smaller sizes and are also used to increase their solubility in aqueous media.