Science and Research Special Topics Report

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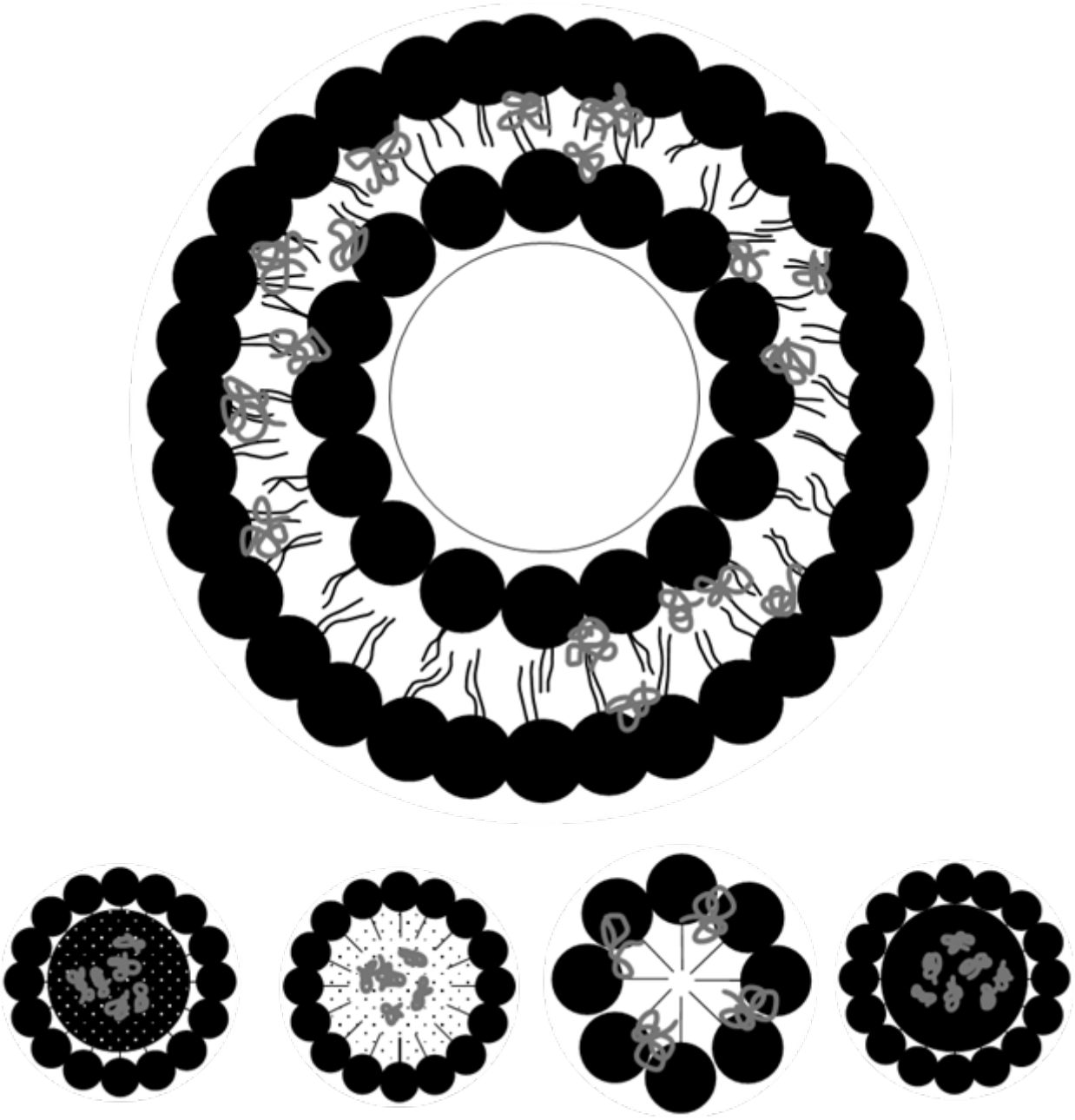
Novel formulations of supplement compounds designed to increase oral bioavailability

In this guide

In this guide

Committee on Toxicity



A schematic diagram of several lipid-based supplement formulations, including liposomes, micelles, emulsions, and lipid nanoparticles. The diagram is shown in black and white. It shows a large spherical shape at the top, with 4 smaller shapes underneath.

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Executive Summary

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Over the past couple of decades there has been an increasing trend within the supplement industry toward the formulation and marketing of bioactive agents (such as vitamins, minerals, and plant metabolites) in novel ways that are designed to increase oral bioavailability. Amongst these formulations are lipid-based preparations such as liposomal, micellar, and emulsions, as well as non-lipid-based preparations including micronisation and co-formulation with polysaccharides. Although these preparations are often marketed as having improved absorption relative to more traditional formulations, there is a lack of evidence and a large degree of uncertainty as to these effects. This is complicated by the heterogeneity of novel formulation types and the lack of data characterising their physical-chemical properties. The effects of supplement formulation on toxicological effects are similarly uncertain and of potential concern, particularly with respect to under-characterised active agents and/or vulnerable populations. Given this situation, the Committee on Toxicity of Chemicals in Food, Consumer Products, and the Environment (COT) have discussed the possible toxicological risks associated with the consumption of supplement compounds formulated in novel ways and the possible increase oral bioavailability of these. The Discussion Paper sets out the physical-chemical

characterisation of several lipid-based and non-lipid-based formulations designed to increase oral bioavailability, the possible physiological mechanisms through which they act, and several case studies reviewing their effects drawn from the literature (curcuminoids, vitamin C, and CBD). The uncertainties surrounding novel bioavailable formulations are also discussed. The Discussion Paper can be found in Annex A and this Special Topics Report provides an overview of the paper's contents and the COT's discussions thereon.

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Physical-chemical properties of novel bioavailable supplement formulations

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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 and which pass readily through the nonpolar lipid bilayer of enterocytes) will be 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 physical-chemical formulation of bioactive compounds (e.g., vitamins, minerals, plant metabolites etc.) can influence their bioavailability (and other

phys/toxico/pharmacokinetic properties). Specifically, alterations in the particulate size of active agents, addition of excipient compounds, and/or encapsulation or emulsification within lipid/oil phases has 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, systems with similar structural, physical, and chemical properties can be achieved using food-grade ingredients and are increasingly observed on the supplement market. By tuning the structural, physical, and chemical properties of these systems, different biological effects can be achieved.

For highly lipophilic compounds the primary strategy that has been used to increase oral bioavailability is the use of lipid/oil-based and amphipathic delivery systems. Most common among these include 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 and which are stabilised interfacial film of surfactants. Bioactive molecules, also referred to as ‘cargo’, dissolved in these oil droplets are maintained in a soluble state within an aqueous media 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 by 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 GI tract. 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.

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.

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COT’s discussion

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The COT discussed the paper presented in Annex A. Members of the Committee considered the emerging market for novel/bioavailable formulations and noted that it is important to remain aware of its current state and possible future developments. In terms of the scientific literature around these formulations, the Committee suggested that if a reporting bias is present - for instance where studies are conducted or commissioned by manufacturers - it is likely to skew findings in the positive direction. Although such bias should be noted, this is not considered to be a significant issue with respect to risk assessment because it

approximates a worst-case scenario.

Members emphasised that although certain points may be drawn regarding novel formulations in general, it is key to assess specific active compounds and their formulation on a case-by-case basis. For instance, in reviewing the case studies presented in the Discussion Paper, the Committee noted that xenobiotics such as curcumin and Cannabidiol (CBD) will differ in their kinetic parameters to essential vitamins such as vitamin C. Specifically, at standard doses vitamin C is fully bioavailable, whereas lipophilic molecules have more scope for increased bioavailability when formulated in novel ways to increase their solubility and uptake. However, Members also noted that the potential toxicity of vitamin A and vitamin D are topical issues, and it may be prudent to be aware of formulations altering their absorption. The formulation of iron and iodine, Members also stated, would be relevant to consider.

Members discussed the challenges in translating from conventional toxicology studies to interpreting the impacts of novel formulations. Members raised the question of potential non-linearity in the dose-responses of these formulations and the point at which increases in area under the curve become toxicologically relevant. Understanding the precise mechanisms driving the alterations in bioavailability, for instance saturation of efflux transporters and/or saturation of metabolic deactivation, are also important for assessing the toxicological implications of novel formulations. Again, this will vary on a case-by-case basis. For instance, whereas increasing the absorbed dose of vitamins and minerals will saturate regulatory mechanisms in the body, non-essential supplements are regulated in different ways. In terms of these toxicokinetic considerations, Members argued that interspecies differences in these processes are also important to consider when evaluating the safety of novel formulations.

In reviewing the potential adverse effects of novel lipid-based formulations Members argued it was important to distinguish between studies conducted in the fed and fasted state. Because absorption requires carrier lipids and bile acids that are modulated by feeding state, Members noted that feeding status may have important effects on toxicokinetics. The interaction between lipid-based formulations and the GI tract was also raised, and it was argued that some formulations may prevent the absorption of dietary nutrients during equilibration in the gut.

The COT discussed the implications of novel formulations for health-based guidance values for specific compounds. Where these values already exist, for example for curcumin, they may not be protective for formulations with increased

bioavailability. Members argued that the critical factor here was understanding how external dose represents the internal dose for standard and novel formulations, and when/if these depart. Here, Members reiterated the issues of cross species differences and extrapolation of no observed adverse effect levels. In cases where kinetic data are available relating to changes in bioavailability, Members suggested this may serve as an additional uncertainty factor that can be applied to Health Based Guidance Value HBGVs for standard formulations of compounds, where they exist. This approach is similar to that undertaken for the lung, already. In the absence of specific kinetic data, Members argued that a conservative approach would be to assume 100% bioavailability of the active compound. Members discussed how these kinds of data are often unavailable, and that the pharmaceutical industry is likely to have more expansive datasets that could aid in these kinds of assessments.

Conclusions and Recommendations

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Conclusions

Within the supplement market, active ingredients continue to be formulated in novel ways that may have important effects on their bioavailability. This may have implications for the toxicological profiles of the supplements in question. Some of the most observed formulations of the market include lipid-based preparations, including liposomes and micelles. However, there are uncertainties

regarding the precise physicochemical characterisation of these formulations. Increases in bioavailability have been demonstrated in the scientific literature for a variety of supplements that are of ongoing interest, including curcumin and CBD.

Recommendations

- Novel formulations and their associated active agents should be assessed on a case-by-case basis.
- The model systems used to assess alterations in toxicokinetics should consider species differences with respect to metabolism.
- The effect of the feeding state (fed vs. fasted) is important to consider when looking at changes in bioavailability.
- Dietary ADIs may not be suitable for characterising the risk from supplements formulated in bioavailable ways.

There are various approaches for considering bioavailability differences in relation to HBGVs that should be addressed on a case-by-case basis.