Other systems to increase bioavailability

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53. Several other systems have been developed to increase the oral bioavailability of poorly soluble/absorbed compounds that do not use lipid-based solubilisation. Such methods include co-formulation with hydrophilic carrier molecules including polysaccharides.

54. Cyclodextrins (CDs) are cyclic oligosaccharides formed by the linkage of D-(+)-glucopytanose units with α-(1,4)-glycosidic bonds. CDs can form complexes with a variety of hydrophobic substances through the incorporation of the entire molecule or part of the molecule into their cavity. The formation of such molecular complexes affects the physicochemical properties of the cargo molecules, including stability, water solubility, and bioavailability (Uekaji and Terao, 2018). Complexing lipophilic supplements with CDs can increase their oral bioavailability, potentially by increasing absorption through the formation of mixed micelles and prolongation of plasma circulation (Terao *et al*., 2006; Uekaji and Terao, 2018).

55. Other molecules that have been used to complex and solubilise lipophilic molecules include soluble fenugreek fibre and galactomannans (Goh *et al*., 2020). These systems act to keep lipophilic molecules solubilised within the GI tract and can be used to form particulate carrier vehicles (Cerqueira *et al*., 2019).

56. Reduction of particle size through micronisation and nanoisation has also been employed to increase solubility of target molecules. Micronisation was developed by the pharmaceutical industry to combat poor bioavailability associated with new chemical entities and has been increasingly adopted within the supplement industry for poorly soluble compounds such as curcumin. Micronisation refers to processes which reduce the average particle size of an active ingredient. Particle size reduction is achieved through comminution and deagglomeration via impact and shear forces, respectively (Kirkwood, 2018). Mechanical milling techniques can produce particles with diameters of around 50-75 µm, whilst ultra-fine grinding methods such as jet milling can result in particles with sizes of <5 µm (Pharmaceutical Technology, 2021).

57. By fragmenting particles into smaller sizes, micronisation increases the surface area to volume ratio area of an active ingredient, thereby increasing its solubility in an appropriate solvent (Savjani *et al*., 2012). As micronisation increases dissolution speed (Bhalani *et al*., 2022), this process can increase absorption and hence the bioavailability of compounds with absorption limited by the rate of diffusion (Oh *et al*., 1995). The poorly soluble nature of many plant-derived compounds has led to investigations of micronisation to increase their oral bioavailability (Xing *et al*., 2017).

58. The production of nanocrystals/nanosuspesions of active ingredients with particles from 200-400 nm can be achieved by wet milling, nancocrystalisation, or spray drying. Like micronisation, nanoisation takes advantage of increased surface area to volume ratio of particle diminution to

increase the solubility of a compound in aqueous media (Tiwari and Takhistov, 2012).