Case study 2: Curcuminoids

In this guide

93. Due to their poor oral bioavailability, novel formulations designed to enhance the oral bioavailability of curcuminoids have been extensively studied. However, it should be noted that “while a large number of such formulations are developed in academia and as garage projects, only a few of them are available on the market in one form or another.” (Jamwal, 2018). Nonetheless, from analysis of the scientific literature, grey and white literature, curcumin appears to be a supplement for which novel formulations designed to increase oral

bioavailability are in the more advanced stages of formulation research, design, commercialisation, and marketisation (compared to, for instance, CBD). The following paragraphs, therefore, relate primarily to studies investigating the pharmacokinetics of commercially available curcuminoid formulations.

Review by Jamwal, 2018

94. Jamwal (2018) published a review of studies investigating the pharmacokinetics of different curcuminoid formulations and calculated their relative oral bioavailability compared to unformulated curcuminoids. Table 5 provides an overview of Jamwal's (2018) review and indicates the relative bioavailability of the various formulations. Relative oral bioavailability values were calculated by Jamwal (2018) using the following formula:

95. (Relative bioavailability = AUC formulation X Dose control)/ (AUC control X Dose formulation).

96. Table 5. Summary of studies investigating effects of curcuminoid formulation on oral bioavailability. Adapted from Jamwal (2018).

Characterisation	**Relative oral bioavailability (positive fold change, from Jamwal, 2018)**	**Reference**
Phytosomal		
Emulsion-based (curcumin, soy lecithin, microcrystalline cellulose)	48	Cuomo *et al*., (2011)
Solid lipid curcumin particles	100	Gota *et al*., (2010)
Fenugreek soluble fibre-based delivery system	15.8	Im *et al*., (2012)

Dispersed micronized curcuminoids.	9.7	Madhavi and Kagan, (2014)
Micronised curcumin	9	Schiborr *et al*., (2014)
Liquid micelles	185	Schiborr *et al*., (2014)
Water-dispersible curcumin complex – Polyvinylpyrrolidone and cellulose based	136.3	Jäger *et al*., (2014)
Turmeric essential oil formulation	6.9 [see corrigendum to Jamwal, 2018]	Antony *et al*., (2008)
γ-cyclodextrin-based formulation	85	Purpura *et al*., (2018)
Colloidal nanoparticles	15.9	Sasaki *et al*., (2011)

97. Overall, the novel formulations summarised by Jamwal (2018) increased the oral bioavailability of curcuminoids compared to administration of unformulated curcuminoids ranging between 6.9 and 185-fold. Of the formulations reviewed, liquid micelles provided the greatest increase in relative bioavailability (185-fold).

98. However, there are important limitations in comparing across these studies. In the first instance, most of the studies reported in Table 5 administered different doses of unformulated vs. formulated curcumin, and thus required dose-normalisation to extrapolate relative oral bioavailabilities. Some studies indicated that curcuminoid pharmacokinetics are non-linear (Kocher *et al*., 2015), suggesting that this method may misrepresent fold-changes in bioavailability between preparations (Flory *et al*., 2021).

99. There was significant variation in the preparative and analytical methods used for detection of plasma curcuminoids and their metabolites. Some of the studies measured levels of free curcuminoids, whereas others quantified conjugated curcumin. Conjugated curcumin is the primary metabolite present in plasma; however, it is less pharmacologically active than the free compound. There were also differences in which metabolites were analysed (curcumin, demethoxycurcumin - DMC, bisdemethoxycurcumin - BDMC, tetrahydrocurcumin - THC), and there is ongoing debate about the relative impact of these metabolites on toxicity. Differences were also apparent in the detection and quantification methods; whilst some studies used high-performance liquid chromatography (stand-alone), others used liquid chromatography-mass spectrometer-based determination.

100. Other important differences related to the clinical trial design including fasting status and food intake after administration of the curcuminoids, which may have important effects on curcumin absorption. There were also differences in the race/ethnicity composition and gender balance of the various cohorts. Some studies have reported sex-differences in the absorption of curcuminoids which is important to consider.

Other studies

101. Several studies not reported by Jamwal (2018) have also investigated the pharmacokinetics of curcuminoid formulations designed to increase oral bioavailability in human subjects. The following paragraphs summarise some of the key findings from these studies. The studies included here were those comparing the pharmacokinetics of oral curcuminoids in standard preparations versus novel formulations in healthy human subjects.

Lipid-based formulations

102. Kocher *et al*., (2015) studied the effects of micellarisation on curcumin pharmacokinetics in healthy volunteers The effects of the adjuvant phytochemicals sesamin, ferulic acid, naringenin, and xanthohumol were also investigated. The study included 23 healthy volunteers administered 98 mg total curcuminoids and was designed as a cross-over trial with one-week washout periods between subsequent treatments.

103. Curcumin, DMC, and BDMC levels were quantified from plasma. The oral bioavailability of total free curcumin was increased by formulation with

phytochemicals, as micelles, and as micelles with phytochemicals by 8-fold, 88-fold, and 73-fold, respectively (comparing the AUC to the control group administered unformulated curcumin). Micellar formulation also increased the AUC of curcumin metabolites DMC and BDMC by 848 and 159-fold, respectively, relative to unformulated curcumin. Overall, micelles were effective at increasing curcumin absorption, and this effect was not further increased by adjuvant phytochemical micelles.

104. Asher *et al*. (2016) used a crossover study design to compare the pharmacokinetics of unformulated curcumin with that of a curcumin-phosphatidylcholine formulation in 12 healthy subjects. Although the physicochemical properties of the phosphatidylcholine complex used were not reported, the Secretariat has assumed this is likely to be a colloidal dispersion of curcumin-phosphatidylcholine. The authors examined plasma and colorectal tissue levels of curcuminoids after administration of 1000 mg unformulated curcuminoids or 385 mg of curcumin-phosphatidylcholine complex once daily for 7 days. Plasma samples were taken immediately prior to the last dose, and then 11 times over 24 hours following the last dose.

105. Tmax was shorter for phosphatidylcholine-curcumin complex versus unformulated curcumin (64 minutes versus 216 minutes for curcumin, respectively). Dose-adjusted AUC0-24h analysis demonstrated that curcumin, DMC, and BDMC (conjugated forms) plasma levels were increased 8.8, 2.9, and 3.0-fold, respectively, with phosphatidylcholine-curcumin versus unformulated curcumin. Curcumin (conjugated and free), DMC (conjugated only), and BDMC (conjugated only) were also detected in rectal mucosa tissue, but their levels were not different between the formulations.

106. Panda *et al*. (2019) investigated the oral pharmacokinetics of curcumin formulated as ‘Curene®’ ®’ versus two reference curcumin formulations – standardised 95% curcuminoids and CP-01, a curcumin formulation containing turmeric volatile oil. Curene® is a proprietary curcumin formulation that, according to the authors, forms an “emulsion similar to liposomes upon contact with the aqueous environment [of] intestinal fluids” (Panda *et al*., 2019), suggesting a S(M)EDDS-like mechanism.

107. Three grams of each curcumin formulation were administered to 12 healthy male subjects split into 3 groups (4 subjects per formulation) and 10 blood samples were collected from point of administration up to 24 hours post-administration. Cmax of free curcumin from the Curene®-curcumin formulation was significantly higher than for control curcumin (1546 vs. 86 and 190 pg/ml for

standardised curcuminoids and CP-01, respectively; *p*0.05), with no change in Tmax. Compared to standardised curcuminoids and CP-01, AUC0-24h was increased by 31 and 14-fold, respectively, (from 207 and 445 pg•h/ml, respectively, to 6303 pg•h/ml; *p*0.05).

108. Briskey *et al*. (2019) compared the oral pharmacokinetics of a novel surfactant, polar-lipids, and solvent-based dispersion curcumin formulation to that of a standard curcumin preparation in 7 healthy human subjects. The so-called LipiSperse® technology is added to an aqueous suspension of curcumin crystals. The surfactant and lipid-based product then forms a coat around the curcumin crystals, coating them, preventing agglomeration, and increasing aqueous solubility.

109. Curcumin formulated with LipiSperse® led to increases in the Cmax and AUC0-6h for curcumin, DMC, and BDMC compared to standard curcumin. In a crossover trial with 5 healthy subjects, curcumin Cmax was increased 3-fold, from 215 to 691 ng/mL (*p*0.05) and total AUC0-6h was increased 2.0-fold*p*0.05). Tmax was unchanged between preparations (1 hour). In a parallel study design with 8 healthy subjects, curcumin total AUC0-6 was 2.3-fold higher in those receiving Lipisperse® curcumin and Cmax was increased by 4.4-fold (151 vs 658 ng/mL; AUC and Cmax *p*0.05).

110. Fança-Berthon *et al*. (2021) compared the oral pharmacokinetics of unformulated curcumin, liquid micellar, phytosomal, and dried-colloidal curcumin formulations in 30 healthy subjects. Different doses of each formulation were used and in accordance with the supplier’s daily recommended doses (1500 mg unformulated curcumin, 1000 mg phytosomal curcumin, 1000 mg liquid micellar curcumin, 300 mg dried-colloidal curcumin). The authors argued that this approach provided meaningful data that could be applied to exposures expected through the real-world use of these products.

111. For non-dose adjusted analysis, the AUC0-24h of total curcuminoids from the liquid micellar formulation were significantly higher than the group receiving unformulated curcumin (control group; *p*0.0001). When AUC0-24h was adjusted for dose, plasma curcuminoids were also significantly increased with liquid micellar, dried-colloidal, and phytosomal curcumin formulations (136, 73, and 13 ng•h/ml/mg, respectively versus 3.7 ng•h/ml/mg for the control group; *p* 0.0001 for each).

112. A 2022 study by Kanae *et al*. investigated the pharmacokinetics of orally administered curcumin in four different formulations: unformulated

curcumin extract, curcumin mixed with squalene, curcumin mixed with docosahexaenoic acid and solid lipid curcumin particles (SLCP). Pharmacokinetics of all four preparations were compared separately in 10 Japanese individuals (5 male and 5 female) >20 years and 65 years of age. A 7-day washout period was observed between trials (Kanae *et al*., 2022).

113. Higher doses of unformulated curcuminoids (260 mg, control group) were administered than for formulated curcuminoids (SLCP: 88mg, squalene: 82 mg, docosahexaenoic acid: 79 mg) and pharmacokinetic parameters were normalised to curcuminoid doses for the various formulations. Conjugated curcuminoids were detected after glucuronidase/β-sulfatase pre-treatment of plasma samples. The Tmax of curcumin was not significantly changed between the formulations (p>0.05), but those of DMC and BDMC were significantly shorter with SLCP, docosahexaenoic acid, and squalene formulations compared to the control group (p0.05).

114. Plasma levels of curcumin and total curcuminoids were higher with the novel formulations at all time points (1 – 8 hours), whilst plasma levels of DMC and BDMC were higher at earlier time points (1 -2 hours), compared to control. The dose-normalised AUC0-8h of curcumin was significantly increased in all the novel formulations compared to the control: 0.43, 0.45, and 0.55 ng/ml.h/mg for solid lipid particles, squalene, and docosahexaenoic acid, respectively, versus 0.19 ng/ml.h/mg for control (p0.01, p0.05, and p0.01, respectively).

115. The dose normalised Cmax of curcumin was also significantly higher for all the novel preparations versus unformulated curcuminoids: 0.09, 0.09 and 0.12 ng/ml/mg for solid lipid particles, squalene, and docosahexaenoic acid, respectively, versus 0.05 for control (p0.05, p0.05, and p0.01, respectively). This amounted to a relative increase of curcumin absorption of 2.2, 2.3 and 2.8-fold for solid lipid particles, squalene, and docosahexaenoic acid preparations, respectively. The AUC0-8h of DMC and BDMC were not different for the novel preparations versus control, whereas their Tmax was significantly shortened for all the preparations (p0.05). The only sex difference observed was a significantly higher dose normalised Cmax for DMC in men administered the standard curcuminoid preparation (p=0.04).

Dispersion technologies

116. Sunagawa *et al*. (2015) investigated the oral bioavailability of Theracurmin® (182 mg), a colloidal submicron-particle formulation of curcumin, in healthy human subjects compared to liposomal (Meriva®; 152 mg) and

micronised curcumin mixed with turmeric essential oils (BCM-95; 279 mg). Theracurmin® is a proprietary technology, and an earlier study investigating this formulation (Sasaki *et al*., 2011) was included in Jamwal's (2018) review, who calculated an increase in relative oral bioavailability over unformulated curcumin of 15.9-fold. Theracurmin® is composed of "curcumin dispersed with colloidal submicron-particles" (Sunagawa *et al*., 2015). This colloidal dispersion is based on the water-soluble polysaccharide gum ghatti that has emulsifying characteristics and can increase the water solubility of lipophilic compounds. To produce Theracurmin®, curcumin powder was added to a gum ghatti water solution, ground by a wet grinding mill, and dispersed by a high-pressure homogeniser (Sunagawa *et al*., 2015).

117. The Sunagawa et al., (2015) study was designed as a 3-way crossover with nine subjects with a 7-day washout period between administration of the different formulations. Theracurmin® resulted in a higher curcumin Cmax (287.2 ng/mL) than BCM-95 and liposomal curcumin of10.7 and 5.6-fold, respectively(p 0.05). AUC0-6h for Theracurmin® was significantly higher than that of BCM-95 and liposomal curcumin by 16.1 and 5.6-fold (p0.05), respectively, whilst the AUC0-24h was 11 and 4.6-fold higher, respectively (p0.05).

118. Panda *et al*. (2021) studied the oral bioavailability of a "novel dispersible" curcuminoid extract compared to a standard curcumin extract. The extract under study was the proprietary CURCUGEN an oleoresin-based turmeric formulation that derives its dispersible properties from turmeric-native polar resins, turmeric essential oils, and turmeric polysaccharides. This formulation preserves the "food-state" ratio of curcuminoids (i.e., the natural ratio of DMC and BDMC), as opposed to standardised curcumin extracts.

119. The oral bioavailability of CURCUGEN was studied in a 2-way crossover trial in 17 healthy male subjects. Plasma levels of free and total curcumin, total DMC, BDMC, curcuminoids, and THC were quantified up to 24 hours post administration. CURCUGEN significantly increased levels of free and total curcumin, and all the curcumin metabolites studied (p0.05). Based on AUC0-24h, plasma levels of all curcuminoids analysed were significantly increased (p0.05): free curcumin (39-fold), total curcumin (50-fold), DMC (44-fold), BDMC (47-fold), total curcuminoids (53-fold), and THC (31-fold).

Comparative studies

120. Flory *et al*. (2021) argued that, owing to non-linear pharmacokinetics, comparing oral bioavailability of curcuminoid formulations administered at

different doses by using the relative AUC method is flawed. A number of studies discussed in the previous sections utilised the relative AUC method, and this may therefore be a consideration when interpreting those studies.

121. Flory *et al*.'s (2021) comparative study compared the effects of different curcuminoid formulations on oral bioavailability using the same administered dose of total curcuminoids between formulations. They compared the pharmacokinetics of seven curcumin formulations designed to increase oral bioavailability with that of native curcumin: micellar, γ-cyclodextrin formulation, phytosomal, submicron-particle, with adjuvants (piperine), with turmeric oil, and liposomal. Preparations were administered at identical doses of curcumin (207 mg) in 12 individuals (6 male, 6 female) per group in a cross-over design.

122. Plasma levels of curcumin were measured over 24 hours. Only the administration of micellar curcumin and γ-cyclodextrin-formulated curcumin led to increases in the AUC0-24h (57-fold and 30-fold, respectively). Micellar curcumin also significantly increased the AUC0-24h relative to γ-cyclodextrin-formulated curcumin (p0.05). Females had significantly higher AUC0-24h than males after uptake of micellar curcumin (p0.05). Phytosomal and submicron-particle curcumin led to non-significant increases in the AUC0-24h of 7.5- and 6.5-fold, respectively.

123. *In vitro* digestive assays demonstrated that sub-micron particles, micellar, and γ-cyclodextrin-formulated curcumin had the highest digestive stabilities (109%, 102% and 73%, respectively). In those same assays, solubility and micellisation efficiency were highest for micellar and γ-cyclodextrin formulations; micellar and γ-cyclodextrin curcumin had solubilities of 80% and 33%, respectively, whilst micellisation efficiency was 55% and 23%, respectively (calculated as "mass curcumin in mixed micellar fraction/mass curcumin in raw material"). Bioaccessibility studies in Caco-2 cells (a human colorectal model) suggested that apparent permeability did not differ between the formulations.

124. Overall, Flory *et al*., (2021) argued that the increased oral bioavailability of micellar and γ-cyclodextrin-formulated curcumin preparations resulted from increased pre-digestive stability and post-digestive solubilisation in gastrointestinal conditions. Increased transport across the epithelium or inhibition of biotransformation and/or epithelial efflux pumps had no effects on oral curcumin bioavailability.

125. The study by Flory *et al*. (2021) suggests that comparing relative oral bioavailability of curcumin formulations administered at different doses may be

misrepresentative. There are also limitations, therefore, in directly comparing between different studies that used different doses. The magnitude of this effect is likely to be exacerbated when there are large differences in doses, and when analysis of plasma curcuminoids is close to or at the limit of detection.

126. Despite these methodological limitations, the literature suggests that novel formulations of curcumin in lipid-based and dispersion systems have the potential to increase oral bioavailability of curcumin and its metabolites. Table 6 provides a summary of the curcumin formulations that led to increased bioavailability in the above studies. The table lists the increase in bioavailability as defined by increased fold changes in Cmax and AUC0-n for curcumin only, as calculated in the respective publications.

Table 6. Summary of curcumin formulations increasing curcumin AUC and Cmax in healthy human studies. Preparations that did not affect AUCs as part of the same study are not included in the table.

Formulation	**Cmax positive fold difference (curcumin)**	**AUC0-n positive fold difference (curcumin)**	**Study**
SLCP	2	2	Kanae *et al*. (2022)
Micelle	216	88	Kocher *et al*. (2015)
Micelle	84	37	Franca-Berthon *et al*. (2021)
Phytosomal	1.2[a]	9	Asher *et al*. (2016)
Phytosomal	203	57	Flory *et al*. (2021)

Aquesome®	18	31	Panda *et al*. (2019)
LipiSperse®	3	2	Briskey *et al*. (2019)
Dried colloidal	23	20	Franca-Berthon *et al*. (2021)
Squalene-curcumin preparation	2	2	Kanae *et al*. (2022)
Docosahexaenoic acid-curcumin preparation	2	3	Kanae *et al*. (2022)
Colloidal submicron	11	11	Sunagawa *et al*. (2021)
Dispersible form (CURCUGEN)	25	50	Panda *et al*. (2021)
γ-cyclodextrin curcumin	56	30	Flory *et al*. (2021)

AUC fold differences were calculated by the secretariat based on presented data. Where available, fold differences were calculated from total curcumin plasma levels, and from the AUC for the longest defined time period. SLCP: solid lipid curcumin particles; n.r.: not reported; [a] values are not dose-normalised and are from administration of 4000 mg standard and 400 mg phytosomal curcumin.