Case study 1: Liposomal vitamin C

In this guide

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79. A significant quantity of the novel formulations on the market appears to be liposomal formulations of vitamin C (see Table 3., above). Liposomal vitamin C supplements therefore provide an informative case study for investigating how novel formulations might impact supplement bioavailability and pharmacokinetics with potential implications for consumers.

80. Due to its potential role in cancer therapy at high doses, a significant amount of attention has been given to the pharmacokinetics of vitamin C. Vitamin C (ascorbate/ascorbic acid) is a hydrophilic compound with complex pharmacokinetics. Its bioavailability is limited by saturable transport mechanisms in the small intestine, its absorption follows a non-linear process, and body levels are dependent on current intakes. Some authors have argued that encapsulation of vitamin C in liposomes may result in a more prolonged release thereby increasing its uptake (Duconge *et al*., 2008). Liposomal encapsulation may also bypass saturable uptake mechanisms via direct transport into the lymphatic system (Duconge *et al*., 2008).

81. Liposomal formulation of vitamin C, therefore, is not designed to increase its solubility in the GI tract, as with lipophilic molecules, but to bypassing its transport rate-limited absorption. This observation underscores the importance of investigating novel/alternative formulations of supplements on a case-by-case basis.

82. Despite its significant presence in the market, however, there are only a handful of controlled studies investigating the oral bioavailability of liposomal vitamin C in humans. A couple of these studies were performed with small sample sizes. These studies and their conclusions are summarised below. The majority of these studies (4/6) were conducted in the last two years, indicating an emergent research interest in formulating supplements with increased bioavailability.

83. In an early study from 2008, Hickey *et al*. investigated the oral pharmacokinetics of standard and liposomal vitamin C. The study contained only two participants, one male and one female. Both subjects received 5 g vitamin C in standard formulation, the female received 5 g and 36 g in liposomal formulation, and the male received 20 g and 36 g in liposomal formulation. These larger doses were administered to test hypotheses about maximum blood levels achievable from oral dosing. Liposomes were composed of phosphatidylcholine (Hickey *et al.,* 2008).

84. In the female subject, the concentration-time curves of plasma vitamin C levels were similar for standard and liposomal formulations (5 g), albeit, with a slightly delayed Tmax (from 100 to approximately 200 minutes). In the male subject, 20 g liposomal vitamin C produced a concentration-time curve with a broader profile than that observed with a 5 g dose of standard vitamin C. In both subjects, administration of 36 g liposomal vitamin C led to plasma levels of approximately 400 µM, higher than that suggested by the NIH (National Institutes

of Health) to be possible from oral dosing at the time of the study, and higher than that achieved via oral dosing or 5 g liposomal vitamin C in the present study. Although pharmacokinetic parameters (Cmax and area under the curve; AUC) were not reported for the 36 g liposomal dose, The concentration-time curve suggested that the liposomal vitamin C resulted in slower onsets to peak levels, and broader profiles, than the 5 g standard dose. The authors argued that these findings indicated a more sustained absorption of liposomal vitamin C owing to the physiological handling of liposomes (Hickey *et al.,* 2008).

85. Davis *et al*. (2016) compared the oral pharmacokinetics of liposomal encapsulated and non-encapsulated vitamin C in 11 older (53±2 years) overweight adults (34.1±1 kg/m^2 BMI). The vitamin C dose was 4 g. Liposomes were made with “mixed natural phospholipids” classified as Generally Recognised as Safe (GRAS) ingredients (GRAS is a designation applied to food ingredients by the United States Food and Drugs Administration. It is a designation that a chemical or substance added to food is considered safe by experts under the conditions of its intended use and is therefore exempt from review as an additive).

86. At two-, three-, and four-hours post-administration, plasma vitamin C levels were significantly higher with liposomal vs. non-liposomal vitamin C (*p* 0.001). The AUC0-4h (the area under the time concentration curve up to 4 hours post administration) was 1.4-fold greater with liposomal vs. non-liposomal vitamin C (10.3±0.9 vs 7.6±0.4 mg/dL h), indicating that oral bioavailability of vitamin C was increased by liposomal formulation. Plasma levels achieved by oral dosing with either standard or liposomal formulation were significantly lower than that achieved by intravenous administration (IV) at all time points (*p*0.001). IV vitamin C achieved a Cmax of approximately 27 mg/dL, compared to approximately 3.5 mg/dL for liposomal and approximately 2 mg/dL for standard vitamin C (*p* values not reported) (Davis *et al*., 2016).

87. Łukawski *et al*. (2020) studied the oral pharmacokinetics of liposomal vitamin C compared to unencapsulated vitamin C in 20 healthy participants. Ten participants received a standard formulation of vitamin C, whilst 10 received a liposomal form. The liposomes used in this study were formulated from soybean phosphatidylcholine. Following administration of 10 g vitamin C, the maximum blood concentration reached (Cmax) was higher in those receiving the liposomal vs. non-liposomal formulation (303 µM vs. 180 µM) and the time taken to reach the maximum concentration (Tmax) was longer, by approximately one hour, from 96 to 180 minutes. The half-life was also longer: >6 hours compared to 4 hours.

The authors concluded that the results “indicate that the presence of liposomes enhances bioavailability of vitamin C.” The authors further suggested that the increased bioavailability of liposomal vitamin C was related to protection from degradation inside the GI tract which provided a sustained reserve of the compound for absorption.

88. Gopi and Balakrishnan (2021) compared the oral bioavailability of liposomal and non-liposomal vitamin C in 24 healthy adults in a cross-over design trial. Participants received 1 g of vitamin C. Tmax was unaffected by formulation (approximately 3.5 hours), whereas Cmax was increased with the liposomal formulation (5.2 versus 1.2 mg/dL). The AUC0-24h analysis also demonstrated an increase with liposomal vitamin C (55.9 versus 31.5 mg•h/dL), whilst half-life was increased from 12.4 to 19 hours with the liposomal formulation.

89. Joseph *et al*. (2021) designed and evaluated the oral pharmacokinetics of a multilamellar surface engineered liposomal vitamin C formulation (in the form of calcium ascorbate). Liposomal surfaces were engineered/modified by impregnation into a fenugreek galactomannan hydrogel in a powder form. All ingredients used were “food grade” and the process was designed to stabilise liposomes from harsh physiological conditions, thereby enabling sustained and increased absorption.

90. Fourteen healthy participants were administered 1 g of vitamin C either in liposomal or non-liposomal forms in a cross-over design. The liposomal formulation resulted in significantly higher plasma vitamin C levels over 12 hours (p0.05). Liposomal vitamin C in tablet and capsule form resulted in a Cmax of 282 and 273 µM, respectively, versus 52 µM for unformulated control. The half-life was also increased from 3.6 hours with unformulated vitamin C to 8.5 and 7.6 hours for tablet and capsule forms of liposomal vitamin C, respectively. The AUC0-12h was increased by approximately 7-fold with the liposomal versus non-liposomal vitamin C preparation. The authors suggested that the larger increase in the AUC observed in their study versus that seen in other liposomal vitamin C studies was due to the enhanced stability of liposomes embedded in a fibre matrix.

91. Jacob *et al*. (2021) also evaluated the oral pharmacokinetics of a fibre-reinforced liposomal vitamin C preparation. The fibre was of turmeric origin. Eight participants were administered 150 mg of vitamin C in liposomal or standard formulations, in a cross over design. Liposomal vitamin C increased the Cmax from 1.2 mg/dL to 6.7 mg/dL and increased the AUC0-24h by 5.9-fold. Like Joseph *et al*. (2021), the authors suggested the enhanced bioavailability of fibre-

reinforced liposomal vitamin C was due to the stability of the formulation under physiological conditions.

92. In summary, liposomal preparations of vitamin C appear to increase oral bioavailability as determined by pharmacokinetic studies. The effects of liposomal vitamin C on the AUC0-n and Cmax in the studies discussed above are summarised in Table 4.

Table 4. Summary of effects of liposomal vitamin C on AUC and Cmax versus non-liposomal preparations.

Study	**Cmax positive fold difference**	**AUC0-n positive fold difference**
Davis *et al*. (2016)	n.r.	1.4
Łukawski *et al*. (2020)	1.7	1.8
Gopi and Balakrishnan (2021)	2.4	1.8
Joseph *et al*. (2021)	5.4	7
Jacob *et al*. (2021)	5.4	5.9

n.r.: not reported. Fold differences in Cmax and AUC0-n were calculated by the Secretariat from the original publications.