EXPERT OPINION

(Soft) capsules of wisdom: preventing myo-inositol malabsorption caused by coffee

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Keywords: absorption, coffee, myo-inositol, soft gel capsule

Expert Opin. Drug Deliv. (2012) 9(10):1177-1179

Development of new drugs or alternative formulations of a pre-existing drug face a number of issues that impact on the efficacy and success of the novel product or novel formulation. One of the major issues is bioavailability. One alternative to classical oral formulations, such as tablet or powder, is the soft gelatin capsule (a.k.a. soft gel capsule) or the liquid (ampoule) preparations. A PubMed search run on July 03, 2012 upon entering "soft gelatin capsule" returned 272 items. The latest paper is by De Grazia et al [1] and it appears in the September issue of this journal, while the earliest paper was published in 1968 [2], both having been published by Italian researchers. (The same search but using the key words "soft gel capsule" returned 152 items.)

The soft gelatin capsules can be used to dispense active compounds that are formulated as a liquid or semi-solid solution, suspension or microemulsion preconcentrate. The formulation of the fill is individually developed to fulfill the following requirements: i) to optimize the chemical stability of the active compound, ii) to improve bioavailability of the active compound, iii) to allow for an efficient and safe filling process, and iv) to achieve a physically stable capsule product.

Soft gel capsules are composed by an outer gelatin shell and by a fill formulation, and the highly specialized manufacturing process is divided in five different steps: i) preparing the gel mass for the outer shell, ii) preparing the fill formulation, iii) encapsulation, iv) drying, and v) packaging. The outer gel mass of the capsule is typically prepared using gelatin, a plasticizer or a combination of plasticizers and water. The gelatins that are used for pharmaceutical or health and nutrition soft capsule products are described by the official pharmacopoeias or are approved by local authorities, with additional physicochemical specifications [3]. After capsule formation, most of the water is removed by drying, leading to finished capsules with a moisture content of 4–10%.

As an endocrinologist with a particular interest for thyroid diseases, I become interested to novel formulation of levothyroxine (L-T4) for the reasons explained below. Excluding the *vexata quaestio* of using the combination of L-T4 with L-T3 as the appropriate therapy for hypothyroidism, there have been no therapeutic advances over recent years in the field of thyroid failure. Indeed, the medical management of hypothyroidism remains anchored to the prescription of L-T4 tablets (for the purpose of this editorial, it is appropriate to mention that prior to the L-T4 tablet there was the thyroid powder). The intestinal absorption of L-T4 is prone to be impaired by a number endogenous and exogenous causes, the latter including drugs and fluids used to swallow the tablet, so that I was faced with clinical cases of L-T4 tablet malabsorption in my daily clinical practice [4-6]. Having become aware of the development of a L-T4 soft gel capsule [7], I was eager to start testing it in the setting of L-T4 tablet malabsorption.

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10.1517/17425247.2012.719495 © 2012 Informa UK, Ltd. ISSN 1742-5247

In collaboration with colleagues, I have demonstrated that the absorption of tablet L-T4 is impaired by plain coffee if coffee is used to swallow the tablet or is taken a few minutes after having swallowed the L-T4 tablet with water [5,6]; no impairment occurred when taking coffee was postponed by 1 hour. Both in patients and in volunteers, the acute oral loading test with tablet L-T4 swallowed with coffee showed that both C_{max} and the area under the curve (AUC) were decreased by about one-third as compared with tablet L-T4 swallowed with water and having coffee 1 hour later [5]. A final confirmation came from *in vitro* studies, whose data were consistent with a sequestering-like effect exerted by coffee [5]. In a recent 6-month duration study (8, paper submitted) on another set of patients with L-T4 tablet malabsorption caused by coffee, using a cross-over methodology (L-T4 soft gel capsules taken with water in the first 3 months, but taken with coffee in the last 3 months), we demonstrated far better absorption of the L-T4 soft gel capsule compared with L-T4 tablets. We used serum TSH as a faithful endpoint of optimal L-T4 intestinal absorption, given that the lower the serum TSH the greater the L-T4 absorption. Indeed, serum TSH levels were low and statistically the same regardless of how the soft gel capsules were swallowed. In contrast, serum TSH had been higher under the tablet regimen, and significantly more so when the L-T4 tablets were swallowed with coffee (or with water but having coffee a few minutes later) compared to when the L-T4 tablets were swallowed with water [8]. Acute oral loading tests in healthy volunteers confirmed more favorable pharmacokinetics indexes for the soft gel capsule compared to the tablet when L-T4 absorption was challenged by coffee [8]. In a head-to-head comparison of L-T4 soft gel capsule with brand tablet L-T4 that was run in volunteers who swallowed the hormone with American coffee, pharmacokinetics indices were more favorable to the capsule [9]. Indeed, C_{max} and $AUC_{0\text{-}12}$ were 12% and 9% greater, while T_{max} was 38.5% (1.5 h) faster.

The soft gel capsule also proved to be refractory to the interference on the tablet L-T4 absorption caused by the proton pump inhibitors both in volunteers [10] and in patients [11], matching the *in vitro* studies that showed a consistent dissolution curve over a wide range of pH values for the soft gel L-T4 compared to brand or generic tablet L-T4 [12]. Interestingly, also another formulation of L-T4, a liquid one in which the hormone is dissolved in ethanol (IBSA Italia s.r.l.), is refractory to the interference caused by the proton pump inhibitors [13]; it is also being tested for refractoriness to coffee interference.

Returning to coffee, it is known to impair the intestinal absorption of inorganic and organic molecules, including drugs such as biphosphonates, antipsychotics, anticancer (for refs. see 6). More recently, the thyroid hormone levothyroxine (L-T4) [5,6] and myo-inositol [1] have been added to list. Because coffee does not change the intragastric pH and times of stomach empting and intestinal transit, it is likely that coffee diminishes the intestinal absorption of the said compounds because it physically interacts with them (for refs. see 5). With hundreds of water-soluble compounds contained in coffee, it may prove difficult to identify the one or those capable of binding L-T4, myo-inositol, and other molecules. For this reason, I think it is not entirely correct that dinto De Grazia et al. [1], throughout the text, Table and Figures, refer to caffeine as the interferer, though they finally admit this limitation in section 5 of their paper [1].

The paper by De Grazia et al. [1] is based on performing acute oral loading tests with 4 g myo-inositol (and measuring its circulating levels for 24 hours post-dose) in 12 healthy nonpregnant women four times, depending on formulation (powder *vs.* soft gel capsule) and liquid for taking it (water *vs.* espresso). The bottom line of this pharmacokinetic article (a genre not quite well reflected by the current title) is twofold. First, already in the baseline situation (viz. water), the soft gel capsule outperformed the powder because C_{max} and $AUC_{0\text{-}24}$ were 93% and 68% greater, respectively. Though no statistical analysis is provided for such comparisons, previous work demonstrated overlapping pharmacokinetics parameters by administering 0.6 g of soft gel myo-inositol or 2 g powder myo-inositol [14]. Because T_{max} values overlapped (with the soft gel value being only 5% faster), the baseline study indicates greater but not quicker intestinal absorption. Second, in the coffee challenge situation, intestinal absorption of powder myo-inositol is affected to a much greater extent than soft gel myo-inositol, though no statistical analysis is provided for such comparisons. Indeed, with the powder, $AUC_{0\text{-}24}$ and C_{max} decreased by 22% and 27% compared with the corresponding baseline values. In contrast, with the soft gel capsule, $AUC_{0\text{-}24}$ and C_{max} decreased by only 11% and 5%. Coffee taking left essentially unchanged the T_{max} values of the soft gel capsules and powder compared to the corresponding baseline values. In the aggregate, all these data indicate two facts. First, the same amount of myo-inositol that is taken with water is absorbed to a greater extent by the intestine if myo-inositol is contained in a soft gel capsule as compared to powder. Second, gelatin is likely to provide a sort of shield that renders myo-inositol less sequestrable by coffee along the myo-inositol journey toward its sites of intestinal absorption.

What comes next? Well, if the pharmacokinetic superiority of the soft gel capsule is clinically meaningful, then pregnant women taking the soft gel capsule myo-inositol with coffee should deliver babies who have lower rates of neural tube defects compared to women who take powder myo-inositol even with water. However, this demonstration requires a specifically designed trial. If results are those theoretically expected, then the current title of this paper [1] is justified.

Declaration of interest

The author has received for free soft gel capsules of L-T4 from IBSA Institut Biochimique SA (Lugano, Switzerland) and liquid oral L-T4 from IBSA Italia s.r.l. (Lodi, Italy) to be distributed to patients in order to conduct the cited clinical studies.The author states no conflict of interest and has received no payment in preparation of this manuscript.

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