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Improved bioavailability of vitamin E with a self emulsifying formulation

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Abstract

A single dose study was conducted to evaluate the bioavailability of a novel self-emulsifying vitamin E preparation, in comparison with that of a commercial product, Natopherol®, available as soft gelatin capsules under fasted condition. The self-emulsifying preparation achieved a faster rate and higher extent of absorption. A statistically significant difference was observed between the values of the two preparations in the parameters AUC, C_{max} and T_{max}. Moreover, the 90% confidence interval of the logarithmic transformed AUC values of the self-emulsifying preparation over those of the soft gelatin capsule product was found to be between 2.1 and 4.1, suggesting an increase in bioavailability of between 210 and 410%. As for C_{max}, the 90% confidence interval was between 2.1 and 3.0. However, no statistically significant difference was observed between the $t_{\frac{1}{2}}$ values estimated from the plasma concentration versus time data of the two preparations. The values are also comparable to those reported in the literature.

Keywords: Vitamin E; Self-emulsifying; Comparative bioavailability

1. Introduction

Alpha-tocopherol, popularly known as vitamin E, is a major lipophilic antioxidant (Ingold et al., 1987). It has been suggested that it plays an important role in preventing cardiovascular diseases and cancer (Newmark and Mergens, 1981; Gey et al., 1987). Due to increased interest in these protective as well as other beneficial effects, many vitamin E preparations have become widely available, often marketed in soft gelatin capsules.

Vitamin E is absorbed via the lymphatic system where it is transported as lipoprotein complex (Machlin and Gabriel, 1983). After oral administration, the vitamin is associated with mixed bile salt micelles in the small intestine to form a fine emulsion before moving across the epithelial cell membrane. It is then incorporated into a lipoprotein unit known as chylomicron or very low-density lipoprotein before leaving the cell. These lipoprotein complexes being too large to pass through the pores of the blood capillaries, are passed into the lymphatic vessels (Palin, 1985).

As bile salts are required in its absorption, vitamin E administered as a dietary supplement in

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the form of soft gelatin capsules, should preferably be taken with food to induce bile secretion (Gallo-Torres, 1970), and not on an empty stomach, but not all consumers may be aware of this fact.

On the other hand, fat soluble vitamins including vitamin E are known to be better absorbed in the presence of surfactants or from emulsified vehicles than from oily preparations (Bateman and Uccellini, 1984). However, a normal emulsion preparation is bulky and also suffers from problems of cracking and creaming on storage. There is thus increased interest in the use of self-emulsifying systems, in which lipophilic drugs such as fat soluble vitamins may be stored in concentrated oil-surfactant solution to be reconstituted with water to form an emulsion immediately before use. Such systems when well formulated will readily form emulsions when added to water with little energy input, such as simple stirring with a spoon, unlike normal emulsion systems which require high energy input for their formation (Pouton, 1985).

The purpose of the present study was to determine the comparative bioavailability under fasted conditions, of a novel self-emulsifying formulation of vitamin E and a commercially available vitamin E product in the form of a soft gelatin capsule.

2. Methods

2.1. Products studied

A self emulsifying preparation containing 400 IU/3 ml α-tocopherol was prepared by mixing Tween 80, Span 80 and vitamin E dissolved in palm oil (333.3 IU/ml) in the following proportions 4:2:4. The other commercially available product (Natopherol®) was in the form of a soft gelatin capsule, each capsule containing 400 IU of vitamin E dissolved in soy bean oil [batch no.: 16491; manufacturing date: 12/97; expiry date: 12/99; registration no: 7470 ABTNEF 10BB, from Abbott laboratories (M) PTE LTD, Singapore].

2.2. In-vivo study design

The study was approved by an Ethics Committee on Bioavailability studies. Eight healthy male volunteers between 22 and 35 years old (mean, 24 years; SD, 5 years) and weighing from 54 to 74 kg (mean, 69 kg; SD, 6 kg), participated in the study after providing written informed consent. All volunteers agreed not to ingest any drug or vitamin preparations for at least 1 week before and during the study period. The study was conducted according to a single dose, two-way crossover design with four subjects in each of the two treatment groups and a washout period of one week between the two phases. The volunteers were randomized to receive orally either one soft gelatin capsule (400 IU) of vitamin E with 200 ml water or 3 ml of the self emulsifying preparation (containing an equivalent amount of vitamin E) which was dispersed in 200 ml water immediately before administration. Both products were administered in the morning (10.00) after a 12 h overnight fast. Food and drinks were withheld for at least 2 h after dosing. Lunch and dinner comprising chicken with rice were served at 4 and 10 h after dosing on the first day of study and again at 9.00, 14.00 and 19.00 the next day. The volunteers were required to refrain from other food during the duration of study. Drinks consisting of mineral water, tea and coffee without milk were allowed ad libitum. Five millilitre blood samples were collected into vacutainers (containing sodium heparin as anticoagulant) at 0 h (before dosing), 1, 2, 3, 4, 5, 6, 7, 8, 10, 14, 18, 24, 30 and 36 h after dosing via an in dwelling cannula placed in a vein of the forearm. The blood samples were centrifuged for 20 min at $2000 \times g$ and the plasma transferred into separate glass containers to be kept frozen until analysis.

2.3. Analysis of plasma α-tocopherol concentration

Plasma level of α-tocopherol was analyzed using a reversed-phase high performance liquid chromatographic method described by Julianto et al. (1999).

2.4. Data analysis

The pharmacokinetic parameters, namely, maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (T_{max}), and total area under the plasma concentration–time curve ($AUC_{0-\infty}$), were estimated from the plasma concentration–time data. The values of C_{max} and T_{max} were obtained directly from the plasma values (Weiner, 1981). The $AUC_{0-\infty}$ was calculated by adding the area from time 0 to time t (AUC_{0-t}) and the area from time t to infinity ($AUC_{t-\infty}$). The former was calculated using the trapezoidal formula and the latter by dividing the last measurable plasma drug concentration by the elimination rate constant (k_e). The k_e was estimated from the terminal slope of the individual plasma concentration–time curves after logarithmic transformation of the plasma concentration values and application of linear regression (Gibaldi and Perrier, 1982). The elimination half-life ($t_{1/2}$) was calculated from the quotient $\ln 2/k_e$. The values of C_{max} and $AUC_{0-\infty}$ obtained with the two preparations were analyzed using an analysis of variance (ANOVA) procedure, which distinguishes effects due to subjects, periods and treatment (Wagner, 1975). The $AUC_{0-\infty}$ and C_{max} values were logarithmic transformed before analysis. On the other hand, the T_{max} values were analyzed using the Wilcoxon Signed Rank Test for paired samples.

3. Results and discussion

Fig. 1 shows the mean plasma vitamin E concentration versus time profiles obtained with two preparations after subtraction of endogenous vitamin E from each subject. It is apparent that vitamin E administered as a self emulsifying preparation had markedly higher plasma levels compared to that given as soft gelatin capsule. The emulsion preparation also appeared to achieve a faster rate of drug absorption as indicated by the more rapid increase in plasma concentrations and a shorter time to reach peak plasma levels. Examination of individual plasma level profiles of the volunteers also revealed that absorption of vitamin E was biphasic in nature, being consistent with that observed by Gallo-Tor-

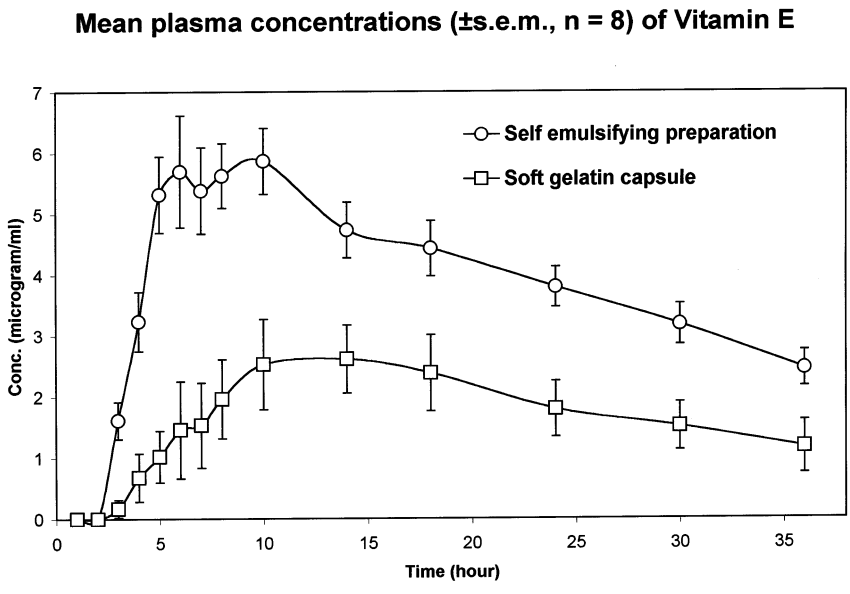

Fig. 1. Mean plasma concentration ($\pm$ S.E.M., $n = 8$) of α-tocopherol as a function of time following oral administration of vitamin E (400 IU) in the form of a self-emulsifying preparation and soft gelatin capsule after substraction of endogenous vitamin E from each subject.

Table 1
Individual C_{max}, T_{max}, $AUC_{0-\infty}$ and $t_{1/2}$ values of vitamin E following oral administration of vitamin E in self-emulsifying preparation and soft gelatin capsule

Subject	Soft gelatin capsules				Self-emulsifying preparation			
	C_{max} (μg/ml)	T_{max} (h)	$AUC_{0-\infty}$ (h · μg/ml)	$t_{1/2}$ (h)	C_{max} (μg/ml)	T_{max} (h)	$AUC_{0-\infty}$ (h · μg/ml)	$t_{1/2}$ (h)
1	7.4	10.0	254.9	20.4	7.6	5.0	275.3	22.6
2	1.0	8.0	10.0	15.4	3.8	10.0	133.2	18.6
3	3.7	14.0	98.6	14.3	6.3	7.0	224.5	22.1
4	2.1	14.0	61.8	20.9	5.5	10.0	196.4	23.3
5	3.3	14.0	117.2	18.6	7.4	10.0	280.3	21.9
6	1.0	14.0	36.1	14.8	7.5	7.0	194.5	14.1
7	2.0	14.0	71.7	21.3	3.7	5.0	118.6	19.0
8	3.5	8.0	106.4	18.5	10.7	6.0	262.6	20.1
Mean	3.0	12.0	94.6	18.0	6.6	7.5	210.7	20.2
SD ±	2.1	2.8	80.0	2.8	2.3	2.2	63.0	3.0

res (1970). In several volunteers, a secondary peak in plasma concentration versus time profile was observed, especially those given the emulsion system. This may be due to the need for mobilization of the other components of the chyclomicra and very-low-density lipoprotein in the absorption process as suggested by Diplock (1985). Additionally, it was also observed that the absorption of vitamin E administered in the capsule form was extremely low in 2 of the 8 volunteers.

An absorption lag time was also observed with both preparations. The self-emulsifying preparation had a lag time of ≈ 2.1 (SD, ± 0.4) h, being significantly shorter ($P > 0.05$) than that of the capsule which has a lag time of 5.0 (SD, ± 2.1) h. The lag time could be attributed to a delay in gastric emptying of the preparations for absorption in the absorptive site in the small intestine. Alternatively, it could be due to the time lapse taken for bile to be secreted since bile salts are required for the vitamin E absorption. Also, the above observations tend to suggest that vitamin E in capsule form required extra time for emulsification before being absorbed. In the case of the self-emulsifying preparation, which was in the form of a ready emulsion, absorption could commence once mixed with the bile salts, leading to more rapid rate and extent of absorption as observed.

Table 1 shows the mean numerical values of $AUC_{0-\infty}$, C_{max} and T_{max} obtained with the self-emulsifying preparation and the soft gelatin capsule. Both the $AUC_{0-\infty}$ and C_{max} values of the self-emulsifying preparation were markedly higher than those of the capsule preparation, while the T_{max} was shorter, indicating a higher rate and extent of absorption. When the parameters were analyzed using the ANOVA procedure described previously, a statistically significant difference was observed between the logarithmic transformed $AUC_{0-\infty}$ ($P = 0.0100$), as well as the logarithmic transformed C_{max} values of the two preparations ($P = 0.0044$). The T_{max} values were also significantly different ($P < 0.05$) when analyzed using the Wilcoxon Signed Rank Test. Moreover, the 90% confidence interval of the logarithmic transformed AUC values of the self-emulsifying preparation over those of the soft gelatin capsule product was found to be between 2.1 and 4.1, suggesting an increase in bioavailability of between 210 and 410%. As for C_{max}, the 90% confidence interval was between 2.1 and 3.0.

The $t_{1/2}$ values estimated from the individual plasma drug concentration profiles of the two preparations are given in Table 1. There was no statistically significant difference ($P > 0.05$) between the values of the two products. Moreover the values are comparable to that reported in the literature (Bateman and Uccellini, 1985).

4. Conclusion

On the basis of the results obtained, it is apparent that the self-emulsifying preparation achieved a higher rate and extent of absorption compared to the soft gelatin capsule under fasted condition. The extent of absorption was increased by almost 3-fold. Absorption of vitamin E also appeared satisfactory in the fasted state when administered as a self-emulsifying preparation, whereas absorption tend to be poor when given as soft gelatin capsule.

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