Solubility of Vitamin E (α-Tocopherol) and Vitamin K_3 (Menadione) in Ethanol−Water Mixture

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Phase behavior of vitamins in aqueous solutions is important in chemical processing and medical and dietary applications. Solubility is reported for two fat-soluble vitamins, vitamin E (α-tocopherol) and vitamin K_3 (menadione), in aqueous mixtures containing ethanol at 33 °C. Both vitamins have very low solubility in pure water owing to hydrophobic repulsion. Addition of ethanol in the water results in a large increase in solubility, mostly due to nonpolar attractive interactions between ethanol and vitamin molecules. For example, by addition of 70 mass % ethanol, vitamin E solubility increases 450-fold and vitamin K_3 solubility increases 170-fold. The enhancement is more pronounced with vitamin E because it is more hydrophobic than vitamin K_3.

Introduction

Vitamins E and K_3 are absorbed by humans through the small and large intestines (Gallo-Torres, 1980; Weber, 1983). This process is initiated by the vitamins' high solubility in fats. In foods, the fat-soluble vitamins are associated with lipids (Kayden and Traber 1986; Weber, 1983). After ingestion, the lipids form fat globules that contain the fat-soluble vitamins (Gallo-Torres, 1970; Hallander, 1981; Imai et al., 1983; Mathias et al., 1981). The lipids also stimulate the release of bile salts and pancreatic juices. This mixture forms mixed micelles with hydrophilic groups of bile-acid molecules facing the aqueous surroundings in the intestinal lumen, and hydrophobic ends facing the interior of the micelles where the dietary lipids and fat-soluble vitamins are dissolved (Weber, 1983; Barrowman, 1984; Carey and Small, 1978; Gibaldi and Feldman, 1970; Nagata et al., 1987). These micelles are then absorbed into the intestinal lining and transported through the body (Gallo-Torres, 1980).

With today's trend of lowering fat intake, fat-soluble vitamin deficiencies are more likely to occur. Vitamin E deficiencies can also occur due to vitamin destruction from modern food-processing practices, such as cooking, canning, freezing, and milling (Diplock, 1985). However, not much is known about vitamin K_3 destruction from food processing (Suttie, 1985). Vitamin excretion is also a concern because as much as 64% of ingested vitamin E is eliminated in the feces (Diplock, 1985; Klatskin and Molander, 1952). Vitamin supplementation may lessen the deficiencies but only if the vitamins are solubilized and absorbed in the digestive tract.

Enhancing the aqueous solubility of vitamins E and K_3 is of interest because of challenges in supplying vitamins to the human body due to the extremely low aqueous solubilities of these vitamins (Browning, 1931). Understanding molecular thermodynamic interactions of vitamin molecules will help the pharmaceutical industry with improved formulations and the chemical industry with improved separation processes (Gupta and Heidemann, 1990). The focus of this work is to study the improvement in vitamin solubility due to the addition of ethanol to the aqueous medium. Ethanol is fully miscible with water, and at the same time it provides a more hydrophobic environment to solubilize these vitamins. Two fat-soluble vitamins, vitamin E (α-tocopherol) and vitamin K_3 (menadione), are studied. These molecules are mostly hydrophobic with some polarity due to hydrogen-bonding sites (Table 1).

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Material

Vitamin K_3 (solid, cat. no. M5625, lot no. 57H0562) and vitamin E (liquid, approximately 95% pure, cat. no. T3251, lot no. 45H1397) were used as received from Sigma Chemical Co. Ethanol, 190 and 200 proof, was obtained from Florida Distillers Co. Deionized, distilled water was used.

Procedure

Vitamin-saturated solutions were prepared with varying mass fractions of ethanol in deionized water. These solutions were allowed to reach equilibrium with excess vitamin in a water-bath thermostated at (33 ± 0.1) °C. The equilibrium was sped up by stirring the samples on a nonelectric magnetic stirrer submerged in the bath. After the 24 h equilibration, samples were analyzed using a UV−vis spectrophotometer (Milton Roy, Spectronic Genesis 2 model) at λ_{max} of 338.3 nm for vitamin K_3 and 291.6 nm for vitamin E. At these respective wavelengths, the extinction coeffcient for vitamin K_3 is 275.5 M^{-1} cm^{-1} and for vitamin E is 254.1 M^{-1} cm^{-1}. At high concentrations, the samples were diluted using ethanol to obtain lower absorbances in the linear calibration range. From each equilibration cell, after the first 24 h, samples were taken at 4 h intervals to confirm that the equilibrium has been reached. Each experiment was repeated three times, which yielded solubility data within 5% error.

Results

The solubility of vitamin E is given in Table 2, and that of vitamin K_3 is given in Table 3. In pure water, these vitamins have very low solubility—20.9 mg/L for vitamin E and 151 mg/L for vitamin K_3—mainly owing to strong hydrophobic repulsion between water and the vitamin molecules.

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Table 1. Fat-Soluble Vitamins Studied

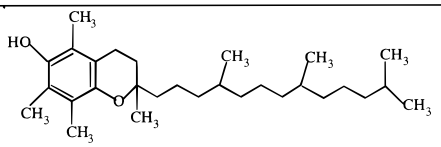
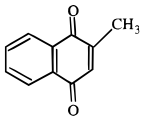
Name	Structure	Molecular Weight
Vitamin E		430.7
Vitamin K_3		172.2

Table 2. Solubility of Vitamin E in Ethanol + Water at 33 °C

ethanol mass fraction	vitamin E	
	mass fraction × 10^6	mole fraction × 10^6
0.00	20.9	0.87
0.10	30.8	1.37
0.20	103	4.90
0.30	272	13.91
0.40	384	21.21
0.48	548	32.22
0.52	736	45.12
0.57	1290	82.55
0.62	2280	152.72
0.66	4690	329.19
0.71	9460	698.02

Table 3. Solubility of Vitamin K_3 in Ethanol + Water at 33 °C

ethanol mass fraction	vitamin K_3	
	mass fraction × 10^6	mole fraction × 10^6
0.00	151	16
0.09	262	29
0.18	550	65
0.27	1250	156
0.36	2950	395
0.45	6630	954
0.54	10620	1651
0.63	15450	2613
0.72	26180	4848
0.81	28490	5840
0.90	29430	6757

Vitamin E molecules have a large hydrophobic alkane chain, with an ether group and a phenol group that can each participate in hydrogen bonding with water. The overall nature of the molecule is hydrophobic, which results in a poor solubility in water. With an addition of 10 mass % ethanol, solubility increases to 1.5-fold. More pronounced effects are observed at higher ethanol concentrations; for example, by an addition of 70 mass % ethanol, solubility is enhanced to about 450-fold owing to attraction between the alkane chains of the vitamin and ethanol molecules.

Vitamin K_3 is less hydrophobic than vitamin E; hence, its solubility in pure water is greater than that of vitamin E. It has two carbonyl groups as polar sites. With an addition of 10 mass % ethanol, solubility increases to 2-fold, and by an addition of 70 mass % ethanol, solubility is enhanced to about 170-fold. Hence, for both vitamins solubility enhancement is very high (Figure 1). Perhaps these data may shed some light on why better health is attributed to a moderate consumption of wine, which is about 10% ethanol.

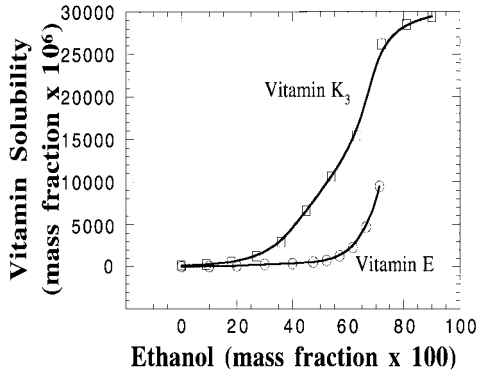


Figure 1. Solubility of vitamins K_3 and E in ethanol + water at 33 °C.

Conclusion

Solubility data are provided for two fat-soluble vitamins, vitamin E (α-tocopherol) and vitamin K_3 (menadione), in aqueous mixtures containing varying amounts of ethanol at 33 °C. Both vitamins have very low solubility in pure water owing to hydrophobic repulsion between water and vitamin molecules. Addition of ethanol in water results in a large increase in solubility. The enhancement is higher for vitamin E because it is more hydrophobic than vitamin K_3. On the basis of solubility data, both vitamins exhibit a highly nonideal thermodynamic behavior.

Literature Cited

Barrowman, J. A. In *Pharmacology of Intestinal Permeation* I; Csaky, T. Z., Ed.; Springer-Verlag: Berlin, 1984; pp 647−689.

Browning, E. *The Vitamins*; Bailliere, Tindall, & Cox: Baltimore, MD, 1931; Vol 1.

Carey, M. C.; Small, D. M. *J. Clin. Invest.* **1978**, *61*, 998−1026.

Diplock, A. T. Vitamin E. *Fat-Soluble Vitamins: Their Biochemistry and Applications*; Diplock, A. T., Ed.; Technomic Publishing Co., Inc.: Lancaster, 1985; pp 171−186.

Gallo-Torres, Hugo E. Obligatory Role of Bile for the Intestinal Absorption of Vitamin E. *Lipids* **1970**, *5*, 379.

Gallo-Torres, Hugo E. Absorption. In *Vitamin E: A Comprehensive Treatise*; Lawrence, J. M., Ed.; Marcel Dekker: New York, 1980; pp 170−193.

Gibaldi, M.; Feldman, S. Mechanisms of Surfactant Effects on Drug Absorption. *J. Pharm. Sci.* **1970**, *59*, 579.

Gupta, R. B.; Heidemann, R. A. Solubility Models for Amino-Acids and Antibiotics. *AIChE J.* **1990**, *36*, 333−341.

Hollander, D. Intestinal Absorption of Vitamins A, E, D, and K. *J. Lab. Clin. Med.* **1981**, *97*, 449.

Imai, J.; Masahiro H.; Shoji, A.; Manabu H. Solubility of dl-α-Tocopherol by Bile Salts, Polysorbate 80 and Egg Lecithin. *Chem. Pharm. Bull.* **1983**, *31*, 4077−4082.

Kayden, H. J.; Traber, M. G. Vitamin E Absorption, Lipoprotein Incorporation and Transfer from Lipoproteins to Tissues. In *Clinical and Nutritional Aspects of Vitamin E*; Hayaishi, O., Mino, M., Eds.; Elsevier Science Publishers: New York, 1986; pp 129−137.

Klatskin, G.; Molander, D. W. The Chemical Determination of Tocopherols in Feces, and the Fecal Excretion of Tocopherol in Man. *J. Lab. Clin. Med.* **1952**, *40*, 802.

Mathias, P. M.; Harries, J. T.; Muller, D. P. R. Optimization and Validation of Assays to Estimate Pancreatic Esterase Activity Using Well Characterized Micellar Solutions of Cholesteryl Oleate and Tocopheryl Acetate. *J. Lipid Res.* **1981**, *22*, 177.

Nagata, M.; Yotsuyanagi, T.; Ikeda, K. Solubilization of Vitamin K_1 by Bile Salts and Phosphatidylcholine-Bile Salts Mixed Micelles. *J. Pharm. Pharmacol.* **1987**, *40*, 85−88.

Suttie, J. W. Vitamin K. In *Fat-Soluble Vitamins: Their Biochemistry and Applications*; Diplock, A. T., Ed.; Technomic Publishing Co., Inc.: Lancaster, 1985; pp 239−249.

Weber, F. Absorption of Fat-Soluble Vitamins. In *Digestion and Absorption of Nutrients*; Bickel, H., Schutz, Y., Eds.; Hans Huber Publishers: Bern Stuttgart Vienna, 1983; pp 55−65.

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