

Discover the Advantage of **EMUSOL® MICELLIZATION**

Emusol © Micellization

Beta-Carotene



Non-micellized Micellized

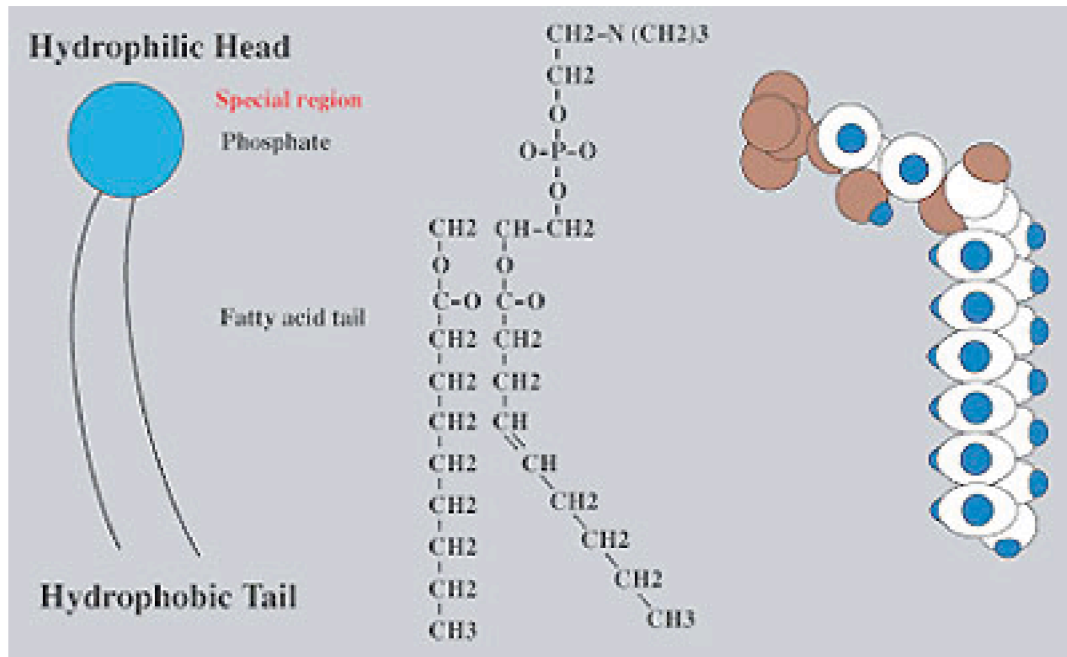


Understanding the Process of Drug or Nutrient Absorption

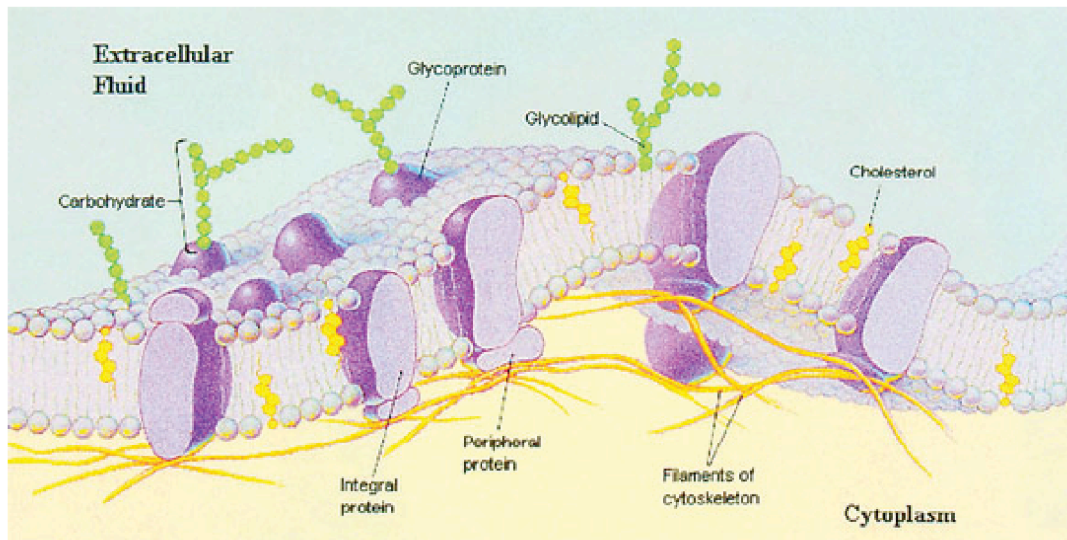
To understand how the micellization process improves the absorption of fat-soluble compounds, one has to understand how drugs/nutrients act in order to have desired therapeutical/nutritional effects. 1, 2

To produce its characteristic effects, a drug must be present in appropriate concentration at its site of action. The extent to which a drug reaches its site of action is called bioavailability. Although it is obviously a function of the amount of drug administered, the concentration at its site of action also depends on the extent of its absorption, distribution and elimination. In order to increase the bioavailability of a drug, one can formulate the dose form that will modify its absorption and distribution process.1, 2, 3

Phospholipid, Figure 1



The absorption of a drug involves its passage across cell membranes. The basic structure of biological membranes is a bimolecular leaf arrangement of lipids as shown in Figure 1, in which the amphoteric lipids and cholesterol are oriented so that the hydrophobic portion of the molecules interact minimizing their contact with water or other polar groups, and polar head groups of the lipids are at the interface with the aqueous environment, as shown in Figure 2.

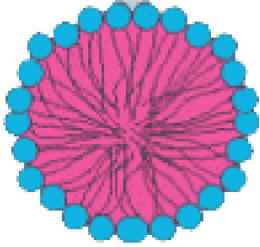


Biological Membrane, Figure 2

At the junction of membrane surface and body fluid, there is a double layer formation. This double layer is aqueous in nature. For a drug to cross the membrane and arrive at its site of action, it must cross this double layer before getting into the membranes. Absorption, regardless of the site, is dependent upon drug solubility in the double layer. The higher the solubility, the higher the absorption, therefore the higher the bioavailability.

How can micellized compounds have better absorption?

When amphoteric surfactant is dissolved in aqueous solution, the molecules of the compound tend to aggregate and form a ball-like structure called micelle: 4



Cell head Big blue hydrophilic “heads” group towards the outside of the ball while little hydrophobic “tails”, which are oil-like, group inside the ball “away” from the solution. Because of the nature of the micellar structure, micellization can solubilize fat-soluble compounds inside the ball and increase solubility of the compounds in the double layer dramatically, hence increasing their bioavailability.

EMUSOL® MICELLIZATION

Emusol Micellized Recognizing the advantages of aqueous preparation of fat-soluble nutrients over oil forms, research during the past years has concentrated on improving the design of new dosage forms that substantially increase the effectiveness of such formulations. Much of this activity has focused on the development of micro-emulsion systems in which an oil is divided into very small droplets (< 0.1 micron) referred to as “micelles”. 4

The use of micellar technology not only improves the efficacy of the product but allows a reduction in the total dose. One of the breakthroughs in nutritional delivery systems is the unique EMUSOL® MICELLIZATION PLUS process. The uniqueness of this process is easily demonstrated by observing the resulting transparent solution when a micellized nutrient is added to water. There is abundant evidence in the scientific literature that fat-solubles are more effectively absorbed from aqueous preparations than from oily forms. 3 However, the real advantage is the increase in amount and rate of absorption.

ENHANCED BIOAVAILABILITY

Several studies have been conducted on the EMUSOL® micelle vitamin preparations to determine the effectiveness of this delivery system when compared with both standard oil forms and other emulsified forms. The studies were conducted in a random crossover fashion with normal healthy individuals varying in sex and age. The following information is a summary of the results:

VITAMIN E FIVE TIMES GREATER ABSORPTION

Platelets play an important role in thrombus formation in arterial vascular walls which may lead to vascular disease. It has been suggested in the scientific literature that vitamin E exhibits anti-platelet activity. 5 However, the plasma level of vitamin E in oil form is found to be very low. The absorption of Vitamin E in oil form is lower than 25% in normal humans. 6

Dosage of 500 IU of d-alpha-tocopheryl acetate were administered to the 12 subjects

and the plasma levels were measured as an increase over baseline levels (19.8 micromoles/liter) at 4 and 24 hours. Figure 3 shows the results of the comparative absorption increases of vitamin E plasma levels of the oil, emulsified and EMUSOL® form at 4 and 24 hours. Table 1 indicates the relative increases in absorption.

Vitamin E absorption, Figure 3

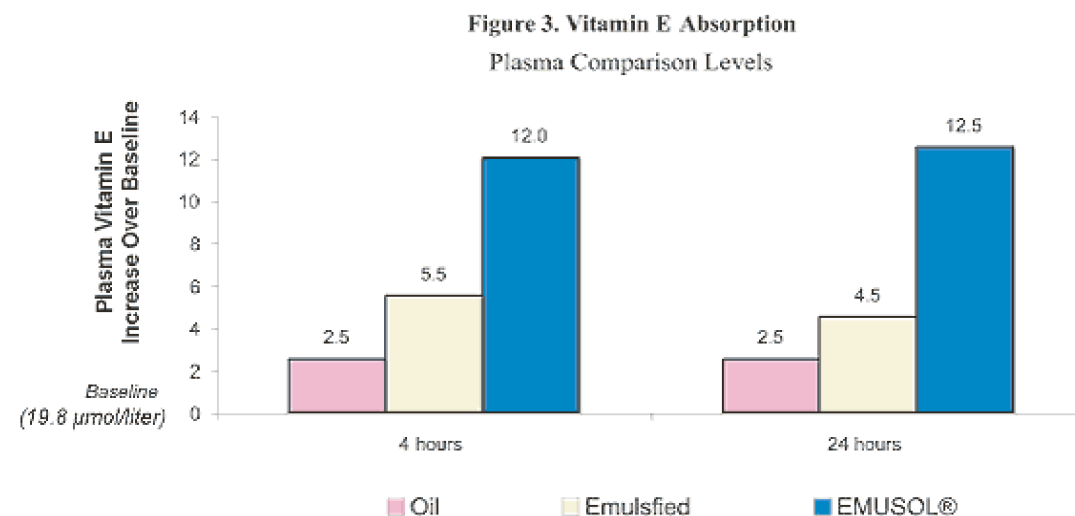


Table 1		
Plasma Vitamin E Levels		
Relative Increases		
	4 Hours	24 Hours
Oil Form	1.0	1.0
Emulsified Form	2.2	2.7
EMUSOL® Form	4.8	5.0

Plasma vitamin levels, Table 1

The data indicates that the EMUSOL® form of vitamin E showed a 4.8 times increase over the oil form at 4 hours and 5.0 times increase at 24 hours. It also showed that the EMUSOL® form increased plasma levels more than twice that of the emulsified form.

OVER FOUR TIMES FASTER ABSORPTION

In a separate study, the rate of the absorption (micromole/liter/hour) was compared using 500 IU of the oil, emulsified and EMUSOL® forms of d-alpha-tocopheryl acetate. Figure 4 shows the results of this study. Table 2 indicates the comparative rates of absorption observed.

**Figure 4. Vitamin E Rates of Absorption
Plasma Comparison Levels**

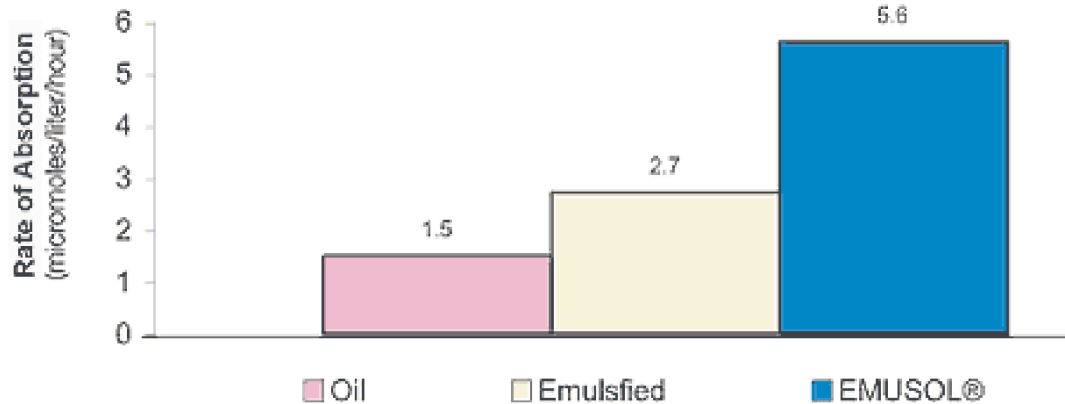


Table 2	
Vitamin E Absorption	
	Relative Increase
Oil Form	1.0
Emulsified Form	1.8
EMUSOL® Form	4.5

Vitamin E absorption, Table 2

The data indicates that the EMUSOL® form of vitamin E is absorbed 4.5 times faster than the oil form. It was also absorbed nearly twice as fast as the emulsified form.

VITAMIN A: FIVE TIMES GREATER ABSORPTION

Human subjects were given 50,000 IU vitamin A palmitate in either an oil, emulsified or EMUSOL® form. The blood plasma levels were measured as an increase over baseline levels (2.675 micromoles/ liter) at 4 and 8 hours. Figure 5 illustrates results while Table 3 provides a summary of the relative increases.

Vitamin A absorption, Figure 4

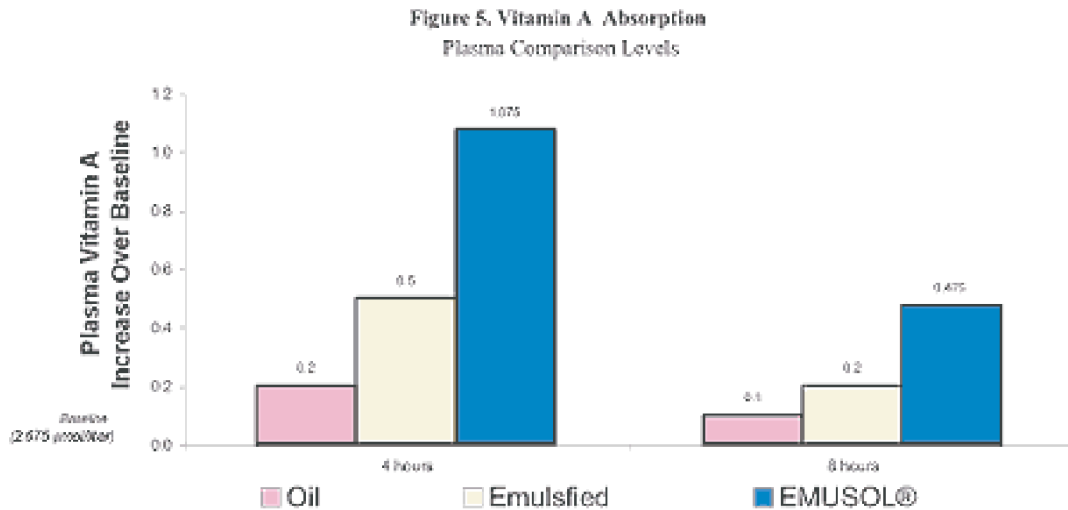


Table 2	
Vitamin E Absorption	
	Relative Increase
Oil Form	1.0
Emulsified Form	1.8
EMUSOL® Form	4.5

Vitamin A plasma levels, Table 3

The data indicates that the EMUSOL® form of vitamin A showed a 5.4 times increase over the oil form at 4 hours and a 4.7 at 8 hours. It also showed that the EMUSOL® form increased plasma levels more than twice that of the emulsified form.

EMUSOL® is a registered trademark of Micelle Laboratories, Inc.

References:

1. Goodman and Gilman's "The Pharmacological Basis of Therapeutics", Eighth Edition, pp 1-83, McGraw-Hill, 1990
2. Thomas M Devlin "Biochemistry with Clinical Correlations" Third Edition, pp 1059-1091, Wiley-Liss, 1993
3.
 - a. Lewis JM, Bodansky O, Birmingham J, Cohan SQ. Comparative absorption, excretion and storage of oily and aqueous preparations of vitamin A. *J Paediatr* 31, 496-508 (1947);
 - b. Kelleher J, Davies T, Smith CL, et al. The absorption of alpha tocopherol in the rat: the effect of different carriers and different dose levels. *Int J Vit Nutr Res* 42, 394-411 (1972);
 - c. Gross S, Melhorn DK. Vitamin E dependent anaemia in the premature infant III. *J Paediatr* 85, 753-759 (1974);
 - d. Jansson L, Londrota M, Tyopponen J. Intestinal absorption of vitamin E in low birth weight infants. *Acta Paediatr Scand* 73, 329-332 (1984);
 - e. Bateman NE, Uccellini DA. Effect of formulation on the bio-availability of retinol, alpha-d-tocopherol and riboflavin. *J Pharm Pharmacol* 36, 461-464 (1984);
 - f. Hittner HM, Speer ME, Rudolph AJ, et al. Retrolental fibroplasia and vitamin E in the preterm infant comparison of oral versus intramuscular administration. *Paediatrics* 73, 238-249 (1984);
 - g. Traber MF, Kayden HJ, et al. Absorption of water-miscible forms of vitamin E in a patient with cholestasis and in thoracic duct-cannulated rats. *Am J Clin Nutr* 44, 914-23 (1986);
 - h. Sokol RJ, Heubi JE, Butler-Simon N, et al. Treatment of vitamin E deficiency during chronic childhood cholestasis with oral d-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS). Intestinal absorption, efficacy and safety. *Gastroenterology* 93, 975-985 (1987);
 - i. Traber MG, Thellman CA, Rindler MJ, Kayden HJ. Uptake of intact TPGS, a water-soluble form of vitamin E by human cells in vitro. *Am J Clin Nutr* 48, 605-611 (1988)
4. Bhargava HN, Narurkar A, Lieb LM. Using microemulsions for drug delivery. *Pharm Tech* 12(3), 46-54 (1987)
5.
 - a. Machlin LJ, Filipski R, Willis AL, et al. Influence of Vitamin E on platelet aggregation and thrombocythemia in the rat. *Proc Soc Exp Biol Med* 149, 275-277 (1975);
 - b. Steiner M, Anastasi J. Vitamin E: an inhibitor of the platelet release reaction. *J Clin Invest* 57, 732-737 (1976);
 - c. Cox AC, Rao GHR, Gerrard JM, White JG. The influence of vitamin E quinone on platelet structure, function and biochemistry. *Blood* 55, 07-912 (1980);
 - d. Tangay CC, Diskoll JA. Effects of vitamin E deficiency on the relative incorporation of 14 c-arachidonate into platelet lipids of rabbits. *J Nutr* 111, 1839-1845 (1981);
 - e. Steiner M. Effects of alpha-tocopherol administration on platelet function in man. *Thromb*

Haemostas 49(2), 3-77 (1983);

f. Kuo P, Wilson, Godstein R. Effect of long-term vitamin E and linoleate supplementation on platelet aggregation in man. *J Am Col N* 3, 244-249 (1984)

6. Klaskin G, Molander DW. The chemical determination of tocopherols in faeces and faecal excretion of vitamin E in man. *J Lab Clin Med* 39, 802-807 (1952)