NanoVehicles - Powered by SMART IDS

Dr. Petro P. Czupiel, PhD

Abstract

The oral route of administration is the most common way to take dietary supplements, which are typically packaged in softgels. However, oil-loving Natural Health Ingredients (NHIs) face significant challenges in reaching the bloodstream due to poor solubility in gastric and intestinal fluids. This five-step process includes: mouth/esophagus, gastric fluid, intestinal fluid, microvilli transport, and systemic circulation. NanoPrime Labs' NanoCurc, a formulated curcumin supplement, addresses this issue using NanoVehicles powered by SMART IDS (Self-Micellization with Advanced Response to Temperature Ingredient Delivery System). This technology enhances curcumin's water solubility from 1.3 mg/L to 289.4 mg/L, allowing for approximately 22,250% more curcumin to be solubilized in gastric fluid. This significant improvement enables the health and mental benefits of curcumin to be achieved.

---

1. Introduction

NanoVehicles are nanostructured vehicles with dimensions ranging from 1 nanometer (one-billionth of a meter) to 15,000 nanometers. They have a hydrophobic (oil-loving) core that can be loaded with multiple oil-loving Natural Health Ingredients (NHIs) and a hydrophilic (water-loving) layer that stabilizes them in water and blood. Currently used in cancer treatment and COVID-19 vaccines, NanoVehicles have the potential to revolutionize the dietary supplement industry by enhancing ingredient delivery into the blood. The key questions are:

1. How can egg- and dairy-free NanoVehicles impact the dietary supplement industry?
2. Where are the NanoVehicles prepared in the body when ingesting NanoPrime Labs' softgels?

Answering these questions can unlock the potential of NanoVehicles in dietary supplements, enabling improved delivery and efficacy of oil-loving NHIs.

2. Oral Route of Administration

The oral route of administration involves taking substances through the mouth, where they are processed and broken down before being absorbed into the body. The journey includes:

a. Mouth and tongue processing
b. Swallowing into the esophagus
c. Stomach acid breaking down substances in the stomach
d. Absorption in the small intestines (90% of absorption)[1]
e. Digestive enzymes and bile from the pancreas, liver, and gallbladder aid in the digestive process
f. Remaining substance travels to the large intestines for water and electrolyte recycling, fermentation, and feces formation[2]
g. Excretion through the rectum and anus

This process, as illustrated in **Figure 1**, highlights the complex journey of substances through the oral route of administration, emphasizing the importance of each step in the digestion and absorption of nutrients and substances.

The oral route of administration begins in the mouth, where both mechanical and chemical digestion pathways occur. Chewing and grinding with our teeth facilitate mechanical digestion, while chemical digestion breaks down carbohydrates and fats with the help of saliva. Saliva contains important electrolytes, mucus, antibacterial enzymes, and digestive enzymes like amylase and lipase, which initiate the digestion of carbohydrates and lipids.[3,4]

The stomach, a 20 cm long J-shaped organ as shown in **Figure 2**, holds gastric fluid with a variable acidic pH between 0.8-3.0.[5] This acidity, due to hydrochloric acid, potassium chloride, and sodium chloride, plays a crucial role in protein digestion. Activated digestive enzymes break down amino acid chains into partially or fully separated amino acids. The gastric fluid also breaks down fibrous plants, fruits, and vegetables, and its volume can range from 13-75 mL in a fasted person, expanding to hold up to 4,000 mL of food.[6–8]

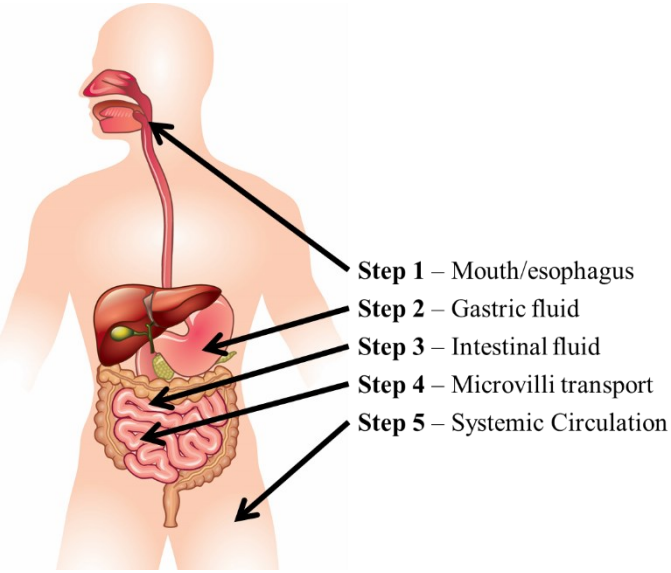

Figure 1. Schematic illustration of the five-step process that all dietary supplements must go through for their intended target of entering our blood. The first step is placing the softgels in the mouth and swallowing through the esophagus. The second step is the digestion and breakdown of the softgels in the gastric fluid found in our stomach. After the gastric fluid step, the broken-up softgels and its contents enter the intestinal fluid where microvilli transport is possible. Systemic circulation in our blood is achieved after transport through the microvilli. Water-loving Natural Health Ingredients (NHIs) can easily travel through each of these five steps. Oil-loving NHIs have an extreme difficulty dissolving in gastric and intestinal fluids, and these problems severely limit the amount of oil-loving NHIs that enter the systemic circulation step.

The gastric mucus releases digestive enzymes, including amylases, nucleases, proteases, peptidases, and lipases, which work on substances they can interact with.[9] Nucleases easily digest nucleic acids, while lipases face challenges with fats and oils due to their poor water-solubility. This hurdle also affects oil-loving NHIs, which will be discussed later.

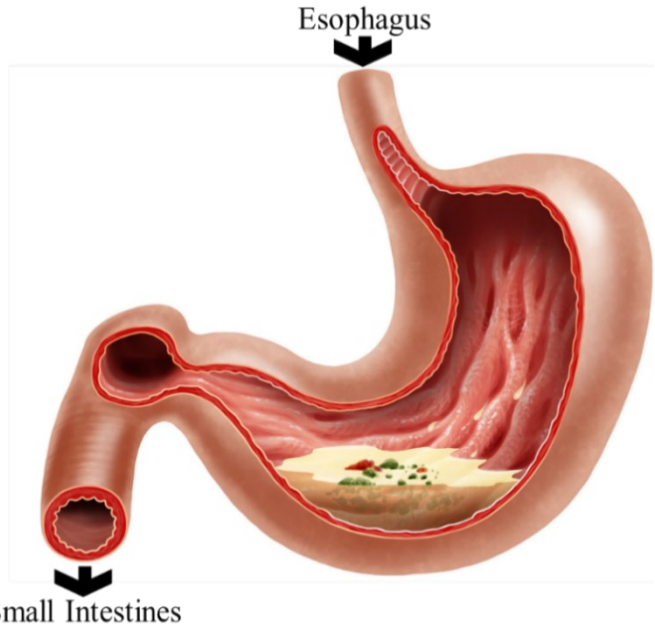

Figure 2. Schematic illustration showing the contents of the J-shaped stomach. The gastric fluid, otherwise known as stomach acid, is acidic with a pH range of 0.8-3.0. The acidic environment along with the digestive enzymes helps to chemically and mechanically digest substances that enter our stomach. All of the digested and undigested substances then flow into the small intestines where the greatest absorption of nutrients and amino acids occurs.

After stomach digestion, substances enter the small intestines, which have an average length of 6.0-6.5 m in adults and 0.2 m in newborns. The small intestines consist of the duodenum, ileum, and jejunum, with the duodenum completing the first phase of digestion. The jejunum increases surface area for absorption through its many folds, and the ileum absorbs bile acids and vitamin B12. Schematic illustrations show the small intestines' structure, including villi and microvilli, which increase absorption surface area.

Small intestines, as illustrated in **Figure 3**, have evolved to optimize absorption, with the pancreas, liver, and gallbladder contributing to the digestive process. Pancreatic juices contain digestive enzymes and neutralize stomach acid, while the liver and gallbladder produce bile salts to break down fats. Bile salts help oil-loving ingredients absorb into microvilli and villi, preventing gallstone formation and dissolving existing ones.

Finally, microvilli transport is the last step before systemic circulation. As shown in **Figure 4,** microvilli interact with water-soluble and water-loving ingredients, making it easy for sucrose to dissolve and absorb but challenging for oil-loving ingredients like CBD. Water-soluble technologies can significantly improve the delivery of oil-loving ingredients into the blood. The next section will compare conventional oil-loving NHIs to NanoPrime Labs' NanoVehicles powered by SMART IDS.

3. 5-step Process for Dietary Supplements

The oral route of administration is the primary pathway for dietary supplements, which are commonly marketed as capsules or softgels. For the purpose of this discussion, we will focus on softgels, which transport Non-Human Identifiable Ingredients (NHIs) into our stomach. **Figure 1** illustrates the five steps that softgels go through to deliver NHIs into our bloodstream. These steps include passage through the mouth and esophagus, gastric fluid, intestinal fluid, microvilli transport, and systemic circulation. Three of these steps are crucial for NHIs to absorb into our blood.

The first step involves softgels being placed in our mouths and traveling through our esophagus. Softgels are designed to withstand breakdown in the

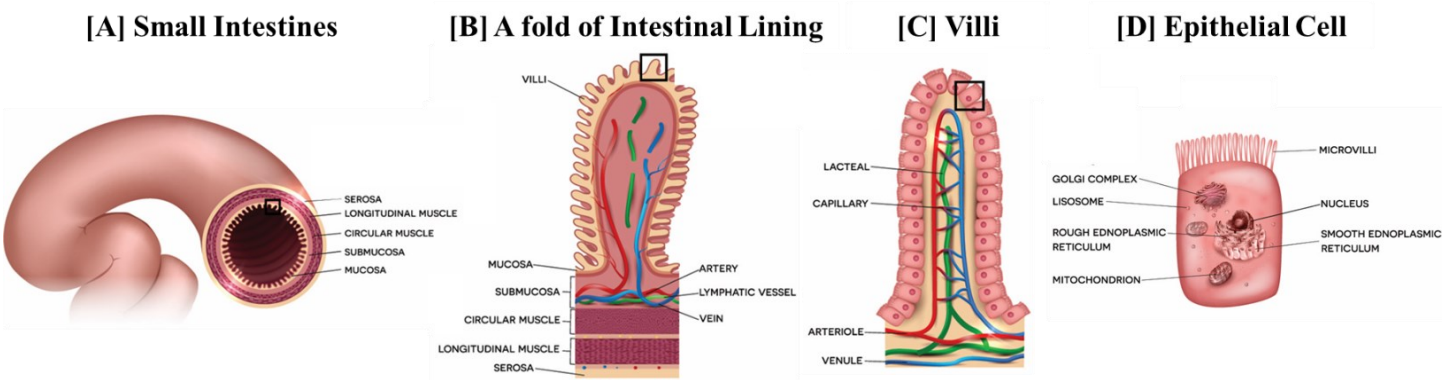

Figure 3. Schematic illustrations showing the contents of [A] small intestines, [B] a fold of intestinal lining, [C] villi, and [D] epithelial cells. The small intestines are surrounded by serosas and longitudinal muscles that cover the circular muscle and enclose the submucosa and mucosa. The black square in [A] is enlarged in [B] to show a fold of intestinal lining that includes many villi lined around the intestinal lining. The black square in [B] is enlarged in [C] to show how one villi is composed of epithelial cells, lacteal, and capillaries that provide that feed and are fed by the venules and arteriole. The black square in [C] is enlarged in [D] to show the complexity of epithelial cells with their smooth and rough endoplasmic reticulum, nucleus, Golgi complex, lysosome, microvilli, and mitochondrion.

mouth and esophagus but break down in the stomach's gastric fluid. Digestion and breakdown of the softgel shell begin in the stomach, where the acidic gastric fluid and elevated body temperature of 37 °C rapidly dissolve the shell. Once broken down, the contents within the softgel begin dissolving in the gastric fluid. Using sugar as an example, the active ingredient sucrose has a high water-solubility of 2,100,000 mg/L. If the softgel contains sugar, it will easily and rapidly dissolve in the gastric fluid. This allows for a seamless transition into the intestinal fluid, where the pH has been neutralized and digestive enzymes have been added. Sugar easily dissolves in the intestinal fluid, facilitating interaction with villi for transport through microvilli and entry into systemic circulation. This example illustrates how the five-step process favors water-loving NHIs. However, oil-loving NHIs face significant obstacles that limit their absorption into systemic circulation

4. Use of Conventional Oil-loving NHIs

Conventional oil-loving NHIs, such as curcumin, are widely available on the market as unformulated powders packaged in softgels. Let's consider a scenario where a health-conscious

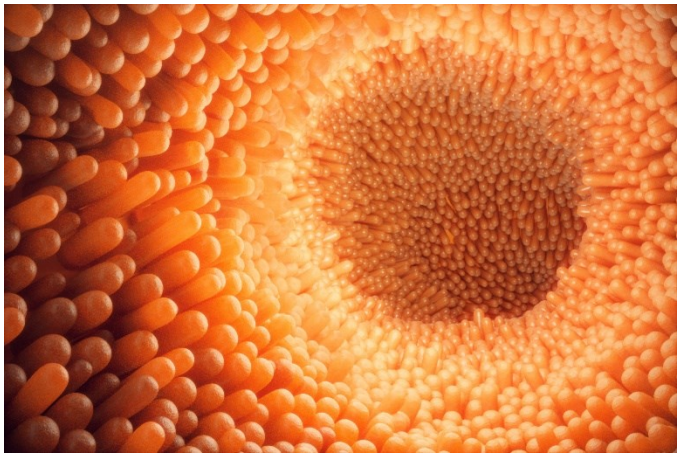

Figure 4. Schematic illustration showing the multiple units of villi that are found along the small intestine pathway. Each of the villi includes many endothelial cells that have microvilli of their own to increase the surface area for absorption.

individual consumes a glass of water (250 mL) before taking a conventional curcumin supplement. The supplement travels through the mouth and esophagus (step 1), and the ingested water helps determine the volume of gastric fluid in the stomach. Given curcumin's water solubility of 1.3 mg/L and the 250 mL of water, the maximum amount of curcumin that can dissolve in the gastric fluid is approximately 0.3 mg. However, this estimate is likely lowered due to the pH and presence of other proteins, salts, and enzymes, which reduce curcumin's water solubility.

As a result, the intestinal fluid step is limited by the maximum potential mass of curcumin that can be dissolved in gastric fluid (0.3 mg). Although the intestinal fluid has a neutralized pH and additional enzymes and bile salts that may contribute to curcumin's solubility, the majority of interactions occur with curcumin that has already solubilized in the gastric fluid step. Minimal amounts of undissolved

curcumin may dissolve in the intestinal fluid, but the largest contribution to solubility occurs in the gastric fluid step. Therefore, less than 0.3 mg of curcumin will interact with the villi for microvilli transport, resulting in significantly limited transport into systemic circulation.

This raises questions about the efficacy of conventional curcumin dietary supplements, which typically deliver 500 mg of curcumin per softgel. Given that only 0.3 mg can dissolve in the gastric fluid, it implies that 99.9% of these products are unable to be utilized and ultimately end up in the toilet. This highlights the need for innovative solutions to enhance the bioavailability of oil-loving NHIs like curcumin.

5. NanoVehicles - Powered by SMART IDS

NanoPrime Labs' NanoVehicles, powered by SMART IDS technology, address the limitations of conventional curcumin products. SMART IDS harnesses the parameters of steps 2-5 in the softgel

intake pathway (**Figure 1**, Section 2 and 3). Focusing on the gastric fluid step, NanoCurc, NanoPrime Labs' curcumin product, boasts a water-solubility of 289.4 mg/L, a drastic improvement over conventional curcumin's 1.3 mg/L. This 223-fold enhancement enables 72.4 mg of curcumin to dissolve in the gastric fluid, compared to only 0.3 mg with conventional curcumin (**Table 1**). NanoCurc ensures a remarkable 22,250% increase in dissolved curcumin, unmatched by conventional curcumin due to gastric fluid volume limitations.

The superior water-solubility of NanoCurc sets the stage for subsequent steps, including intestinal fluid and microvilli transport. With 72.4 mg of curcumin dissolved in the gastric fluid, NanoCurc prepares a substantial amount for interaction and transport through the microvilli, ultimately leading to systemic circulation. The significant differences in water solubility across the oral route of administration are tabulated in **Table 1**. NanoCurc's ability to dissolve 72.4 mg of curcumin in the gastric fluid step scientifically outperforms conventional curcumin, delivering a substantial 22,250% increase. This breakthrough ensures the health and mental benefits of curcumin are achievable. The power of SMART IDS will be further explored in our next white paper.

	Conventional Unformulated Curcumin	NanoPrime Labs' NanoCurc
Step 1 - Mouth/esophagus	0.0	0.0
Step 2 - Gastric fluid	1.3 mg/L	289.4 mg/L
Step 3 - Intestinal fluid	<1.3 mg/L	<289.4 mg/L
Step 4 - Microvilli transport	<1.3 mg/L	<289.4 mg/L
Step 5 - Systemic circulation	Very Low	Very High

Table 1. Tabulated solubilities of conventional unformulated curcumin were directly compared to NanoPrime Labs' NanoCurc. Acknowledging that solubility in gastric fluid is an important bottleneck for this five-step process, it is easy to obverse the inefficiency of conventional unformulated curcumin. Conventional unformulated curcumin can dissolve in gastric fluid at a maximum concentration of 1.3 mg/L and this value decreases in steps 3 and 4. The superiority of NanoPrime Labs' NanoCurc is easily observed as the solubility of NanoCurc at the gastric fluid step is 289.4 mg/L. The very high solubility of NanoCurc is held through the intestinal fluid step and optimizes the microvilli transport for maximized systemic circulation.

6. Conclusions

The oral route of administration is a pathway where substances are ingested through the mouth, and dietary supplements in softgels commonly utilize this route. As discussed earlier, the oral route involves various organs and both chemical and mechanical digestion processes. Softgels containing oil-loving Non-Human Identifiable Ingredients (NHIs) undergo a five-step process to reach their final destination in the bloodstream. This process consists of passage through the mouth and esophagus, gastric fluid, intestinal fluid, microvilli transport, and systemic circulation. However, oil-loving NHIs face an inherent chemical challenge due to their extremely low solubility in gastric and intestinal fluids.

Curcumin serves as a case study, with a comparison between conventional, unformulated curcumin and NanoPrime Labs' NanoCurc, which contains NanoVehicles powered by SMART IDS technology. Conventional curcumin has a water solubility of 1.3 mg/L, which decreases in gastric and intestinal fluids. In contrast, NanoPrime Labs' NanoCurc boasts a water solubility of 289.4 mg/L, ensuring a remarkable 22,250% increase in curcumin solubilization in the gastric fluid. This significant enhancement enables the achievement of curcumin's health and mental benefits.

7. References

(1) McClements, D. Structured Emulsion-Based Delivery Systems: Controlling the Digestion and Release of Lipophilic Food Components. *Adv. Colloid Interface Sci.* **2010**, *159* (2), 213–228. https://doi.org/10.1016/j.cis.2010.06.010.

(2) Shishu; Kamalpreet; Maheshwari, M. Development and Evaluation of Novel

Microemulsion Based Oral Formulations of 5-Fluorouracil Using Non-Everted Rat Intestine Sac Model. *Drug Dev. Ind. Pharm.* **2012**, *38* (3), 294–300. https://doi.org/10.3109/03639045.2011.602407.
(3) Yuan, Q.; He, Y.; Xiang, P.-Y.; Wang, S.-P.; Cao, Z.-W.; Gou, T.; Shen, M.-M.; Zhao, L.; Qin, W.; Gan, R.-Y.; Wu, D.-T. Effects of Simulated Saliva-Gastrointestinal Digestion on the Physicochemical Properties and Bioactivities of Okra Polysaccharides. *Carbohydr. Polym.* **2020**, *238*, 116183. https://doi.org/10.1016/j.carbpol.2020.116183.
(4) Tiwari, M. Science behind Human Saliva. *J. Nat. Sci. Biol. Med.* **2011**, *2* (1), 53–58. https://doi.org/10.4103/0976-9668.82322.
(5) Homayun, B.; Lin, X.; Choi, H.-J. Challenges and Recent Progress in Oral Drug Delivery Systems for Biopharmaceuticals. *Pharmaceutics* **2019**, *11* (3). https://doi.org/10.3390/pharmaceutics11030129.
(6) Axson, J. L.; Stark, D. I.; Bondy, A. L.; Capracotta, S. S.; Maynard, A. D.; Philbert, M. A.; Bergin, I. L.; Ault, A. P. Rapid Kinetics of Size and pH-Dependent Dissolution and Aggregation of Silver Nanoparticles in Simulated Gastric Fluid. *J. Phys. Chem. C* **2015**, *119* (35), 20632–20641. https://doi.org/10.1021/acs.jpcc.5b03634.
(7) Jeliński, T.; Przybyłek, M.; Cysewski, P. Natural Deep Eutectic Solvents as Agents for Improving Solubility, Stability and Delivery of Curcumin. *Pharm. Res.* **2019**, *36* (8), 116. https://doi.org/10.1007/s11095-019-2643-2.
(8) *Volume of a Human Stomach - The Physics Factbook*. https://hypertextbook.com/facts/2000/JonathanCheng.shtml (accessed 2021-04-01).
(9) Ménard, D. Development of Human Intestinal and Gastric Enzymes. *Acta Paediatr.* **1994**, *83* (s405), 1–6. https://doi.org/10.1111/j.1651-2227.1994.tb13390.x.

8. Disclaimer

The information in this white paper is for education and general information purposes only and has not been evaluated by the Food and Drug Administration (FDA). The information in this white paper is not implied or intended to be a substitute for professional medical advice, diagnosis, or treatment. The information and products mentioned are not intended to mitigate, treat, diagnose, prevent or cure any medical condition. Please refer to the label on the dietary supplement bottle or website for interactions, cautions and safety data. You are strongly encouraged to consult with a qualified health care provider (pharmacist, registered dietitian, family physician, naturopath, etc.) if you have any health concerns or questions and interests about the use of dietary supplements. Any specific mention of a brand name is not a direct or indirect endorsement of that product.