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RESEARCH ARTICLE

Biotechnology of Nanostructures Micronutrients Vitamins for Human Health

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ABSTRACT

Nowadays, nanotechnology is used as a way to increase bioavailability and decrease the side effects of drugs and nutrients. Micronutrients and nutraceuticals such as vitamins, carotenoids, polyunsaturated fatty acids and polyphenols are classes of food ingredients that are essential for human health and well-being. These compounds are rarely added purely to the targeted food application but rather in encapsulated, solid, dry product forms with added functionalities such as improved stability, bioavailability or handling. Development of new strategies, like nanocarriers, that help to promote the access of neuroprotective molecules to the brain, is needed for providing more effective therapies for the disorders of the Central Nervous System (CNS). Polymer–lipid hybrid nanoparticles, encapsulating vitamin D3 and vitamin K2, with improved features in terms of stability, loading and mucoadhesiveness were produced for potential nutraceutical and pharmaceutical applications. Recently, nanoformulations that include nanovesicles, solid-lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, and polymeric nanoparticles have shown promising outcomes in improving the efficacy and bioavailability of vitamin E. Active targeting of nanoparticles loaded with vitamin D to cancer cells.

INTRODUCTION

History of vitamins

In 1912, the Polish biochemist Casimir Funk (1884 - 1967) coined the term vitamins. The discovery of vitamins as essential factors in the diet was a scientific breakthrough that changed the world! Already in 1906, Frederick Gowland Hopkins indicated that "no animal can live on a mixture of pure protein, fat and carbohydrate" – this started the search for "growth factors" in food. The Dutch physician Christian Eijk- man found that a constituent of rice bran can prevent a beriberi-like disease in chickens and Gerret Gryns was the first scientist to adopt the deficiency theory for the etiology of this disease. He stated that the disease breaks out when a substance necessary for the metabolism is lacking in the food.

In 1912, Casimir Funk isolated a bioactive substance from rice bran which was at first given the name "vita-amine". Funk realized that this substance could cure chickens and human patients from beriberi. He published a landmark paper "The etiology of the deficiency diseases" and stated that all "deficiency diseases can be prevented and cured by the addition of certain preventive substances, the deficient substances", for which he proposed the name "vitamins" [1]. Two years later in 1916, the American biochemist Elmer V. McCollum introduced capital letters to differentiate between vitamin A, vitamin B, vitamin C and vitamin D. Later, vitamin E and vitamin K were added and it was realized that a food containing vitamin B can

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contain more than one factor and a further differentiation into vitamin B_1, vitamin B_2 and so on was applied.

These observations and findings facilitated the experimental research in the following years enor- mously. The next three decades were full of scientific breakthroughs in the understanding of the role of vitamins and by 1941; all 13 vitamins had been discovered and characterized. These are now classified as either water- (e.g. vitamin C) or fat-soluble (e.g. vitamin A), as listed in table 1. The scientific break- troughs were honored with twelve Nobel Awards to 20 Nobel Prize winners. The Nobel Award in Chemistry 1928 was given to Adolf Windaus for his studies on the constitutions of the sterols and their connection with the vitamins. This was followed by the Nobel Prize in Medicine and Physiology in 1929 jointly to Christiaan Eijkman for the discovery of the anti-neuritic vitamin and to Sir Frederick Gowland Hopkins for the discovery of the growth-stimulating vitamins.

Already in the 1940s, authorities had started to establish dietary standards and nutrient requirements (recommended daily allowance) for the optimal intake of vitamins depending on age, gender and risk groups. In order to secure a sufficient intake of vitamins for the full population, a number of coun- tries implemented fortification programs of staple food; today food fortification is established in more than 60 countries. Examples are the fortification of flour or sugar with vitamin A especially in low-income countries, the fortification of flour with folic acid in the US, Canada and Latin American countries, the fortification of margarine with vitamin A and D or the fortification of milk and juices with vitamin D.

Table 1: Main groups of micronutrients and nutraceuticals.

Micronutrients & Nutraceuticals Water-soluble vitamins	Major formulation challenge
Vitamin B_1 (Thiamine) Vitamin B_2 (Riboflavin) Vitamin B_3 (Niacin) Vitamin B_5 (Pantothenic Acid) Vitamin B_6 (Pyridoxine) Vitamin B_7 (Biotin) Vitamin B_9 (Folate) Vitamin B_{12} (Cyanocobalamin) Vitamin C (Ascorbic Acid)	chemical stability (oxidation, hydrolysis, light, temperature, pH), sensory (taste), discoloration
Fat-soluble vitamins [2]	
Vitamin A (Retinol, Retinyl Esters, Retinal, Retinoic Acid), Carotenoids, Vitamin D (Ergocalciferol, Cholecalciferol), Vitamin E (A-Tocopherol, Tocotrienol), Vitamin K (Phylloquinone, Menaquinone)	chemical stability (oxidation, hydrolysis, light, temperature, pH), solubility in water, bioavailability
Polyunsaturated Fatty Acids (PUFAs)	
e.g. omega-3 fatty acids such as Docosahexaenoic Acid (DHA)	chemical stability (oxidation), sensory (smell, taste)
Polyphenols [3,4]	
e.g. Epigallocatechin Gallate (EGCG), resveratrol	chemical stability (temperature, oxygen, light, pH), bioavailability, sensory (taste)
Minerals	
e.g. Fe, Zn, Ca, Mg	sensory (taste)
Plant extracts [5,6]	chemical stability, sensory

The World Bank's assessment of fortification was: "probably no other technology available today offers as large an opportunity to improve lives and accelerate development at such low cost and in such a short time". Today, there is a wide consensus amongst scientists about adequate vitamin intake and the relation to health and healthy aging. Science continues to provide new approaches and insights on the role of vitamins and to demonstrate that "the identification of the role of vitamins was one of the most important contributions of science to mankind".

Subjects and methods

Oral delivery of vitamins: Vitamins are organic micronutrients that are essential to the human body and important for the maintenance of normal metabolism, cellular regulation, growth, and development. Humans require 13 dietary vitamins [7]. For people at risk of vitamin deficiency, an oral supplement is generally the first treatment [8]. However, some vitamins have low oral bioavailability due to degradation, poor GI transport, and low water solubility. Thus, it is essential to develop novel forms of oral vitamins to improve absorption.

Vitamin A: Vitamin A is essential to human health. Encapsulation in lipid nanoparticles was used to overcome vitamin A poor water solubility in beverages. This work aimed to develop and characterize lipid nanoparticles, containing vitamin A, for food fortification, assuring its stability and oral bioaccessibility. Lipid nanoparticles optimized for the oral administration of vitamin A using the hot homogenization method. The nanoparticles subjected to conditions used in food processing suffered no changes in their size or vitamin content. In vitro assays simulating gastrointestinal digestion suggested that the nanoparticles are not altered in the stomach, and the biocompatibility of the formulations showed no toxicity in fibroblasts. With the developed nanoparticles 80% of the added vitamin reached the intestine in the digestibility assay, demonstrating suitability as a nanotechnology application in the food research for the food industry.

Fat-soluble vitamins have important roles in the synthesis and degradation of nutrients, immune function, homeostasis, and growth [9]. The A vitamins are unsaturated fat-soluble organic compounds, including retinol, retinal, retinoic acid, and some provitamin A carotenoids (Figure 1A). Oral carotenoids, which are bioconverted to vitamin A, are often recommended for disease prevention. β-carotene is the most commonly used carotenoid in functional foods and pharmaceutical products, because of its strong provitamin A and antioxidant activities. The current Recommended Dietary Allowance (RDA) of vitamin A is 600 μg Retinol Activity Equivalents (RAE) per day for adult females and 800 μg for adult males [10].

Vitamin B: Vitamins B and C are water-soluble molecules that function as cofactors for many enzymes. The vitamin B

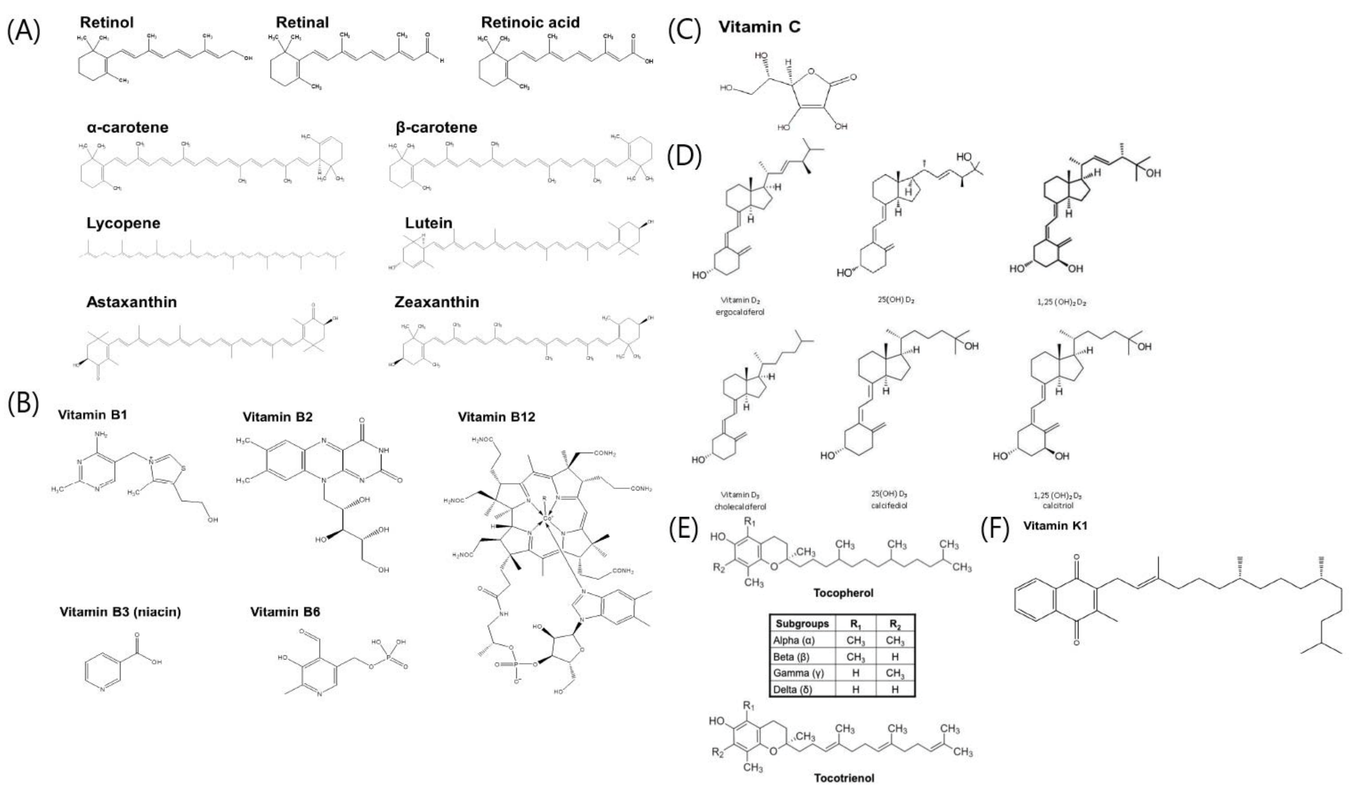

Figure 1 Chemical structures of (A) vitamin A; (B) vitamin B; (C) vitamin C; (D) vitamin D; (E) vitamin E; and, (F) vitamin K.

group consists of B1, B2, B3, B5, B6, B7, B9, B12, and related derivatives (Figure 1B). Among these, B1, B2, B3, B6, and B12 play important roles in disease prevention.

Vitamin C: Vitamin C is the only water-soluble vitamin not in the vitamin B group (Figure 1C). It is one of the most essential vitamins and it has roles in many physiological processes, including immune response and iron absorption [11]. Vitamin C is abundant in many fruits and vegetables, such as mango, kiwi fruit, papaya, lettuce, tomato, and strawberry. Vitamin C is also a strong antioxidant that can reduce oxidative stress.

Vitamin D: Vitamin D (VD) is one of the lipophilic vitamins. The most important forms of VD are cholecalciferol (Vitamin D3, VD3) and Ergocalciferol (vitamin D2, VD2). The chemical structure of ergocalciferol, cholecalciferol, and their active derivatives are given in figure 1D. VD3 is the main form and is available in some natural dietary products (egg yolk, flesh of fatty fish, and fish liver oils), food fortified with VD, and many forms of dietary supplements. VD2 is of plant origin and present in low amounts, e.g., in some mushrooms. VD2, being less potent than VD3, is rarely present in commercial preparations and fortified food. Despite that, it is a good alternative for vegans and vegetarians. However, the main source of VD is endogenous synthesis from 7-dehydrocholesterol in the human skin after sun exposure. Part of VD is stored in adipose and muscle tissue, and part of it gets hydroxylated. Independent of the source, VD3 and VD2 act as hormone precursors since they require two stages of metabolism: First to 25-hydroxy VD (25(OH)D, calcidiol) in the liver; then to 1α, 25-dihydroxy VD (1,25(OH)D, calcitriol) in the kidney [12].

Vitamin D has two major forms: D2 and D3 (Figure 1D), each of which the body converts into the bioactive calcitriol (25-dihydroxyvitamin D). Ultraviolet irradiation of ergosterol in plants leads to the formation of vitamin D2, and ultraviolet radiation of 7-dehydrocholesterol in human skin leads to the formation of vitamin D3. Vitamin D is also obtained from foods, including egg yolk, fish, and milk. Vitamin D has important roles in the mineralization of bone and teeth, due to its regulation of calcium and phosphorus homeostasis [13]. There is also evidence that vitamin D supplements can prevent malignancies, cardiovascular diseases, osteoporosis, and diabetes.

Vitamin D deficiency is a highly prevalent condition, present in approximately 30% to 50% of the general population. A growing body of data suggests that low 25-hydroxyvitamin D levels may adversely affect cardiovascular health. Vitamin D deficiency activates the renin-angiotensin-aldosterone system and can predispose to hypertension and left ventricular hypertrophy. Additionally, vitamin D deficiency causes an increase in parathyroid hormone, which increases insulin resistance and is associated with diabetes, hypertension, inflammation, and increased cardiovascular risk. Epidemiologic studies have associated low 25-hydroxyvitamin D levels with coronary risk factors and adverse cardiovascular outcomes. Vitamin D supplementation is simple, safe, and inexpensive. Large randomized controlled trials are needed to firmly establish the relevance of vitamin D status to cardiovascular health. In the meanwhile, monitoring serum 25-hydroxyvitamin D levels and correction of vitamin D deficiency is indicated for optimization of musculoskeletal and general health.

Vitamin E: Vitamin E belongs to the family of lipid-soluble vitamins and can be divided into two groups, tocopherols and tocotrienols, with four isomers (alpha, beta, gamma and delta). Although vitamin E is widely known as a potent antioxidant, studies have also revealed that vitamin E possesses anti-inflammatory properties. These crucial properties of vitamin E are beneficial in various aspects of health, especially in neuroprotection and cardiovascular, skin and bone health. However, the poor bioavailability of vitamin E, especially tocotrienols, remains a great limitation for clinical applications. Recently, nanoformulations that include nanovesicles, solid-lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, and polymeric nanoparticles have shown promising outcomes in improving the efficacy and bioavailability of vitamin E.

Vitamin E has been proven to have a wide range of therapeutic effects beyond its well-known antioxidant properties. Despite these promising effects, vitamin E, especially tocotrienol, is not well recognised for therapeutic interventions due to its poor bioavailability. In vivo studies have shown that the concentration of tocotrienols in plasma is lower in the presence of alpha-tocopherol due to the lower binding affinity towards α-TTP. Furthermore, tocotrienols have a relatively shorter $t_{1/2}$ than tocopherols, which also contributes to poor bioavailability.

Generally, vitamin E is made up of a chromanol ring and an isoprenoid or phytyl side chain. Tocopherols have a long and saturated side chain, while tocotrienols differ from tocopherols by the presence of unsaturated double bonds on the side chain. Chemical structures of tocopherol and tocotrienol. The different vitamin E isoforms are determined based on the presence and position of methyl group(s) as side chains on the chromanol ring (Figure 1E). This also explains the higher affinity of tocotrienols to the lipid membrane compared to tocopherols [14].

Molecules in the vitamin E group, which function as antioxidants and free radical scavengers, include four tocopherols (α,β,γ, and δ) and four corresponding unsaturated tocotrienols (Figure 1E). The three vitamin D transporters (SR-BI, NPC1L1, and CD36) also function in vitamin E absorption. An increasing number of investigations have attempted to increase vitamin E bioavailability by the use of nanoparticles. Encapsulation of vitamin E within nanoparticles can impede its interactions with other fat-soluble vitamins, which would otherwise inhibit vitamin E absorption.

Vitamin K: Based on its source, vitamin K is classified as plant-derived vitamin K1 (phylloquinone) or animal/bacteria-derived vitamin K2 (menaquinones) (Figure 1F). Vitamin K1 is a procoagulant that is used in cases of hemorrhage, and vitamin K2 has roles in the regulation of blood clotting factors, namely prothrombin and five other proteins (Factors VII, IX, and X, and proteins C and S) [15].

The chemical structures of the vitamin D and its active derivatives are presented in figure 1D, whereas the fate of VD in the body is presented in figure 2. It is considered that most people are insufficient or deficient in VD due to a lack of sun exposure, extensive use of sunscreens, which block VD synthesis, and poor dietary intake. Maintaining recommended serum levels, i.e., 30-60 ng/mL of 25(OH)D3, can be achieved through vitamin supplementation or food fortification without changing lifestyle to avoid impaired skeletal and overall health [16].

RESULTS AND DISCUSSION

Vitamins and oxidative stress

The most powerful water-soluble antioxidant in the organism is Vit C, present physiologically as ascorbate anion [18,19]. Mammals can synthetize VitC in the liver, with the exception of humans, primates or guinea pigs that need to consume it from the diet. In all the cases, ascorbate passes from cerebrospinal fluid to deep brain structures by diffusion, and a Sodium-Dependent Transporter (SVCT2) concentrates ascorbate intracellularly [18,20]. The most important neuroprotective action of ascorbate is exerted by regulation of extracellular glutamate levels. Excessive glutamate release and accumulation produces neurotoxicity [21], and the activation of extracellular glutamate uptake involves the release of ascorbate to the extracellular medium by a glutamate-ascorbate heteroexchange membrane transporter [18]. The extracellular concentration of ascorbate in brain tissue is maintained homeostatically at the expense of intracellular stores [20,22], and ascorbate may also offer protection at the intracellular compartment [23].

VitE is the most effective chain-breaking, lipid-soluble antioxidant in cellular membranes [24], and is one of the major scavengers of radical-oxygenated species in nervous cells [25]. It traps free radicals and breaks the chain reaction, preventing the propagation of lipid peroxidation. This reaction produces a tocopheroxyl radical, which requires ascorbate for its regeneration back to reduced VitE [24,26]. Thus, the antioxidant effect of VitE is potentiated by co-administration with VitC. In fact, previous studies carried out in animal models [27] and in humans [28] reported a more powerful neuroprotective effect when the two vitamins are administered together.

VitE is taken from the diet, incorporated into lipoproteins, and delivered systemically [24]. Such distribution is possible due to the α-Tocopherol Transfer Protein (α-TTP), which

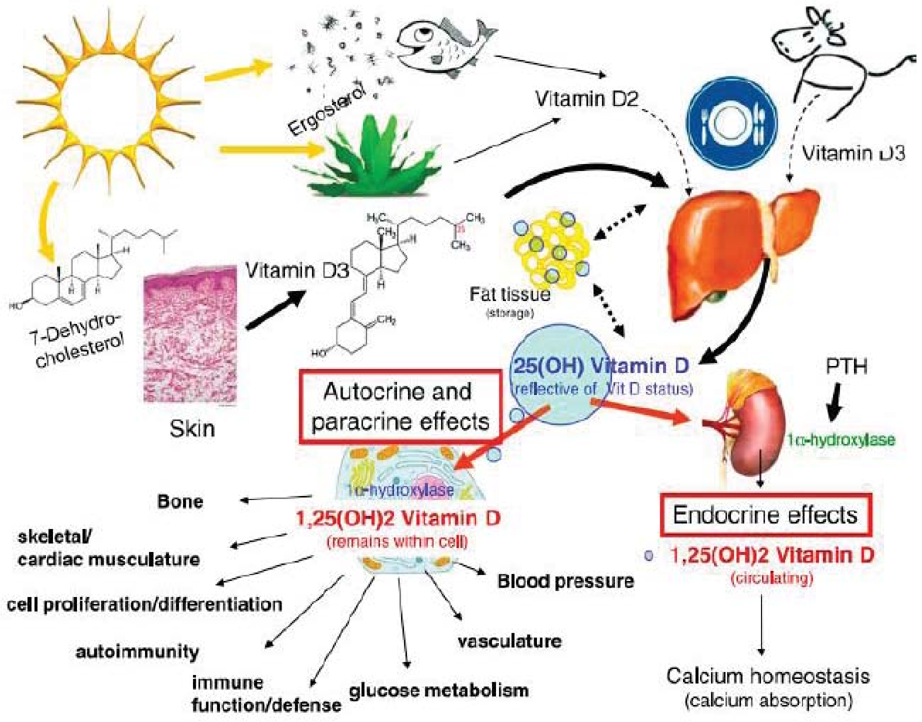

Figure 2 Scheme of vitamin D sources, fate in the body, and pleiotropic actions of 1,25-dihydroxy vitamin D (calcitriol), the active form of vitamin D. Reproduced with permission from [17]; published by Elsevier, 2011.

controls the hepatic uptake of VitE. α-TTP is present in many organs, including the brain [29], but its effect on VitE transport remains unclear.

Thus, VitC and VitE are transported into neurons by different carrier proteins, and accumulated by separate systems that act synergically [30]. A recent work [31] reports the brain distribution of SVCT2 and α-TTP, which display specific patterns that remain unchanged with age. Besides, they are present mainly in neurons but not in astrocytes, and this could contribute to explain the selective responses observed in neurons against OS [32].

VitC and VitE have been successfully tested in several in vitro and in animals models studies in order to improve aging-related process [23,33-36]. However, the results obtained from human trials are not always consistent. Low levels of VitC and VitE, as well as other antioxidants, have been observed in plasma of individuals with Alzheimer's disease and mild cognitive impairment [37,38], which has led to the suggestion that supplementation with antioxidants could delay or reduce cognitive impairment. The results of the several trials that have already been carried out in the last decades failed to reach a consensus by the role of these vitamins in the treatment of aging and related disease [39-44]. This can be due, at least in part, to the heterogeneity (e.g., genetic variations as well as differences in diet, lifestyle and environmental factors) of the human population and the difficulty in finding true controls [24], as well as the inherent variability in amounts of VitE present in regular diets.

Micronutrients, nutraceuticals and nanoliposomal carriers: A formulation challenge

Vitamins are a class of micronutrients that play a significant role in human growth. The major part cannot be synthetized in the human body or is formed in very little amount. Hence, the importance to provide vitamins in adequate quantities through a diet of fortified food and/or supplements suitably produced by delivery systems [45,46]. Indeed, in their naked form, vitamins are highly susceptible to degradation and possess poor bioavailability, thus it is essential to wrap vitamins in protective materials in order to prevent their deterioration during both food processes and their uptake in the organism, [47] i.e. to enhance their solubility, stability and targeting profile [48].

Micronutrients administration by fortification of staple and complementary foods is a followed strategy to fight malnutrition and micronutrient deficiencies and related pathologies. There is a great industrial interest in preparation of formulations for joint administration of vitamin D3 and vitamin K2 for providing bone support, promoting heart health and helping boost immunity. To respond to this topic, in this work, uncoated nanoliposomes loaded with vitamin D3 and K2 were successfully prepared, by using a novel, high-yield and semi continuous technique based on simil-microfluidic principles. By the same technique, to promote and to enhance mucoadhesiveness and stability of the produced liposomal structures, chitosan was tested as covering material. By these way polymer–

lipid hybrid nanoparticles, encapsulating vitamin D3 and vitamin K2, with improved features in terms of stability, loading and mucoadhesiveness were produced for potential nutraceutical and pharmaceutical applications. To prevent and/or treat micronutrients deficiency several strategies are currently adopted, such as fortification of staple and complementary foods, provision of supplements [49]. For these latter purposes encapsulation of micronutrients is, under production point of view, the main approach to ensure suitable dosing, loaded molecules stability and bioavailability.

The understanding that micronutrients are essential for human and animal growth and health [50] and that they have to be part of the diet was a major stimulus for nutrition science. Research was ex- tended also to nutraceuticals and health ingredients such as polyunsaturated fatty acids, oily plant ex- tracts and fruit powders that provide certain health benefits (but are not essential) [51]. Subsequent to the recognition of the vitamins and the discovery of their function it became clear that breakthroughs in the production, formulation and application would have to be achieved in order to allow them to be used by humans and animals. This inspired scientists in pharmaceutical companies in Europe and the US to develop synthetic routes and formulation technologies. The first production of a vitamin on a technical scale was achieved by Hoffmann-La Roche in 1934 for vitamin C based on a combined fermentation and chemical process developed by Tadeus Reichstein. In the following years all vitamins became available via chemical synthesis, fermentation or extraction from natural materials. Industrial production was not the complete solution yet, and new challenges arose with the incorporation of micronutrient and nutraceuticals in end-user applications such as tablets, vitamin waters, beverages, yoghurts and other foodstuffs.

Especially lipids and fat-soluble vitamins [2] are difficult to add to food products (e.g. to a hydrophilic en- vironment such as a beverage), and are often chemically unstable to, e.g. oxidation, hydrolysis, light and heat [52,53]. New technologies had to be explored and again know-how and formulation competencies of pharmaceutical companies gave the basis for the development of vitamin forms. This offered opportunities to provide vitamins for humans and animals for optimal growth and health. Therefore, micronutrients and nutraceuticals are nowadays rarely sold in pure form and are mostly delivered in microencapsulated product forms to protect the active ingredient from the surrounding environment [54-57]. Thereby the stability and shelf-life of the compounds are prolonged and they can be released in a controlled and tailored manner. Further benefits of microencapsulation processes include easier handling, improved sensory properties with respect to appearance and taste and uniform dispersion of low-concentrated actives [58]. Innovation in colloid and nanosciences facilitates the development of product forms for different applications. Progress in formulation results from close cooperation between basic sciences carried out at universities and applied science in industry. However, the knowledge of formulation is often a special expertise of companies, protected by patents and not available in textbooks.

Developments in nutraceuticals and functional foods nanotechnology

Nanoliposomal carriers and chitosan coated nanoliposomes, encapsulating vitamin D3 and vitamin K2, were both successfully produced by the simil-microfluidic technique, with the advantages of massive production, operating at environmental conditions and continuously.

Investigation [59] on uncoated nanoliposomes showed high encapsulation efficiencies, especially for vitamin K2 (EE: 95%) due to its more hydrophobic character. Uncoated K2 and D3 loaded nanoliposomes have been shown poor mucoadhesive characteristics thus chitosan coating was performed to overcome this issue. The coverage efficacy was proven to be dependent on chitosan concentrations and on kind of enwrapped vitamin in the liposomal structure. In this study, the best coverage was obtained with 0.01% w/v chitosan for unloaded and D3-loaded liposomes, and with 0.005% per K2- loaded liposomes. Moreover, the best chitosan coverage for each liposomal formulation has led an increase of the entrapment efficiency from 88% to 98% for D3-loaded liposomes and from 95% to 98% for K2-loaded ones. This enhancement is occurred, reasonably, due to the fact that during the coating process, chitosan covers the surface of the liposomes and fills the gaps in the hydrophobic bilayer.

Nanotechnology is an opening up for new perspectives in all scientific and technological fields. Among these applications, herbal drugs and nutraceuticals [60] are the fast growing fields in nanoresearch. A variety of new herbal formulations and nutraceuticals like polymeric nanoparticles, nanocapsules, nanoemulsions, transferosomes and ethosomes has been reported using bioactive, plant extracts and food materials. New herbal drugs and nutraceuticals are reported to have remarkable advantages over conventional formulations of plant actives and extracts which include enhancement of solubility, bioavailability, expansion of stability, sustained delivery, improved tissue macrophages distribution, protection from toxicity, enhancement of pharmacological activity and protection from physical and chemical degradation.

Nutraceuticals are foods and food constituents that provide health benefits beyond basic nutrition, but many nutraceuticals show poor bioavailability. Applications of nanotechnology have granted to overcome the challenges and technical barriers related to the solubility, bioavailability, stability and delivery of bioactives from foods. The rapid growth of nutraceutical nanotechnology carries great promise to provide new and effective functional foods as a tool for preventing and possible even bringing a cure to some non-communicable diseases. Numerous studies are already reported in different types of preparative methods of nanomaterials in the field of nanotechnology for herbal drug delivery and nutraceuticals (Figure 3A) [61-65].

Nanotechnology platforms are widely being used to create delivery systems for nutraceuticals and bioactive natural products with poor water solubility. Some of the extensively studied nutraceutical nanomaterials are discussed here. Figure 3B depicts the potential applications of nanotechnology in nutraceuticals.

Hydrophobins (Hyd) used for nanoencapsulation of nutraceuticals for food enrichment is very much interesting they bid to hydrophobic materials like Vitamin D3 (VD3). Hyd provided excellent protection to VD3 against degradation. Moreover, Hyd were found to be promising nanovehicles of hydrophobic nutraceuticals for food and beverages enrichment [66]. Folic acid was encapsulated with two different matrices (Whey Protein Concentrate (WPC) and a commercial resistant starch) and two different encapsulation techniques (spray drying and electro-spraying). Greater encapsulation efficiency was observed using WPC as encapsulating matrix. Electrospraying is a promising method in the food industry for encapsulation applications [67]. Emulsification-Diffusion Method (EDM) is an excellent alternative to prepare nanocapsules from food constituents. Formation of nanocapsules with DL-α-tocopheryl acetate and β-carotene has confirmed the versatility and reproducibility of the EDM when batches with different materials are prepared under optimal conditions [68].

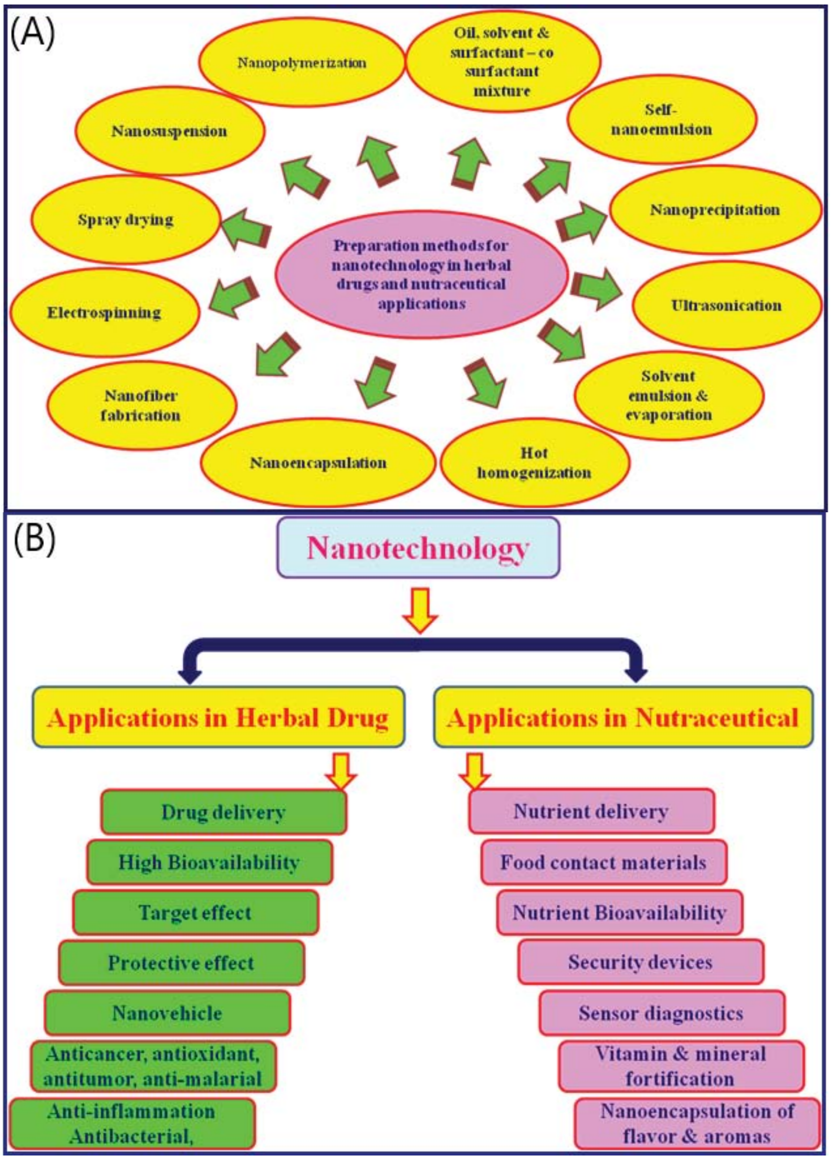

Figure 3 Schematic representation of (A) various methods of preparation of nanotechnology in herbal drugs and nutraceuticals. (B) Applications of nanotechnology formulated herbal drugs and nutraceuticals.

VD3 was entrapped in Whey Protein Isolate (WPI) nanoparticles prepared with different calcium concentration. Composition of nanoparticles with calcium can perform a compact structure providing reduction of VD3 degradation during storage time. WPI nanoparticles containing VD3 can be used for enriching of clear or non-clear drinks such as herbal beverages, fruit drinks or low fat food [69]. Dual nutraceutical nanohybrids consisting of Folic Acid (FA) and calcium were prepared based on Layered Double Hydroxide (LDH) structure through exfoliation-reassembly hybridization method FA/LDH nanohybrids showed higher contents of essential nutrients in human health and they could be considered as dual nutraceutical nanomaterials [70]. Hosseini, et al. [71] were explored the potential application of the protein-polysaccharide soluble nanocomplexes as delivery systems for nutraceuticals in liquid foods. The complexation between B-Lactoglobulin (BLG) and four nutraceutical models including β-carotene, folic acid, curcumin and ergocalciferol was investigated under different conditions and the low water soluble nutraceuticals were successfully entrapped within electrostatically stable nanocomplexes [71]. Nanocarriers made with hempseed oil or a blend of amaranth and hempseed oils were investigated for a concomitant encapsulation and release of the carotenoids enriched plant extract. The nanocarriers have a great potential for clinical applications as a new delivery system for other lipophilic plant extracts enriched in bioactive compounds [72]. A novel lipid-free nano-CoQ10 system formulated and stabilized by various surfactants and the bioavailability of CoQ10 was evaluated by oral administration of CoQ10 formulation in Sprague-Dawley rats. The formulation can be an effective vehicle for improving oral bioavailability of CoQ10, it was confirmed by the observation of significant increase in the maximum plasma concentration and the area under the plasma concentration time curve [73]. The bioavailability of heptadecanoic acid and CoQ10 was investigated for the influence of droplet size and oil digestibility by a rat feeding study. The developed nanoemulsion based delivery system has increased oral bioavailability of lipophilic nutraceuticals [74]. Food grade biopolymers, proteins and polysaccharides can be used to create a diverse range of delivery systems suitable for encapsulating, protecting and delivering lipophilic functional components such as omega 3-fatty acids, conjugated linoleic acid, oil-soluble vitamins, flavors, colorants and nutraceuticals [75]. Novel organogel-based nanoemulsions were developed for oral delivery of curcumin and improvement of its bioavailability. In vitro lipolysis profiles revealed that the digestion of nanoemulsion was significantly faster and more complete than the organol. Organogel based nanoemulsion can be used for oral delivery of poorly soluble nutraceuticals with high loading capacity, which has significant impact in functional foods, dietary supplements and pharmaceutical industries [76].

Supercritical assisted injection in the liquid antisolvent process has been used for the production of α-tocopherol nanoparticles suspensions and produced NPs can be used as supplementation and as an antioxidant in food, cosmetics and pharmaceutical industries [77]. The potential of native and thermally modified Lactoferrin (LF) to form co-assembled vehicles for the delivey of (-)-Epigallocatechin-3-Gallate (EGCG) was investigated by Yang, et al. [78] LF-EGCG nano and submicrometer particles could act as protective vehicles for EGCG and a beneficial aid for the development of controlled release of other bioactive materials. The effect of Clove Essential Oil (CO) and its major constituents, eugenol, formulated in water-based microemulsion was studied on fatty liver and dyslipidemia in high-fractose-fed rats. CO and Eugenol Microemulsion (EM) produced significant improvement in fatty liver and dyslipidemia with consequent protection from cardiovascular disease and other complications of fatty liver [79]. Two nutraceutical induction methods, DMSO dilution in water and acidification were used for enzymatically synthesis of dextran NPs to entrap hydrophobic nutraceutical, the isoflavone genistein. The DMSO method was found to be more suitable for inclusion of genistein in dextran, resulted in a high genistein load and high percentage of nanosized particles [80].

Lipid nanoparticles to improve oral delivery of vitamins

In this section, we highlight recent progress in the development of lipid nanocarriers for vitamin delivery [81]. In addition, the same lipid nanocarriers used for vitamins may also be effective as carriers of vitamin derivatives, and therefore enhance their oral bioavailability. One example is the incorporation of D-α-Tocopheryl Polyethylene Glycol Succinate (TPGS) as the emulsifier in lipid nanocarriers to increase the solubility and inhibit P-glycoprotein (P-gp) efflux. We also survey the concepts and discuss the mechanisms of nanomedical techniques that are used to develop vitamin loaded nanocarriers.

The chemical environment and enzymes in the Gastrointestinal (GI) membrane limit the oral absorption of some vitamins. The GI epithelium also contributes to the poor permeability of numerous antioxidant agents. Thus, lipophilic vitamins do not readily dissolve in the GI tract, and therefore they have low bioavailability. Nanomedicine has the potential to improve the delivery efficiency of oral vitamins. In particular, the use of lipid nanocarriers for certain vitamins that are administered orally can provide improved solubility, chemical stability, epithelium permeability and bioavailability, half-life, nidus targeting, and fewer adverse effects. These lipid nanocarriers include Self-Emulsifying Drug Delivery Systems (SEDDSs), nanoemulsions, microemulsions, Solid Lipid Nanoparticles (SLNs), and Nanostructured Lipid Carriers (NLCs). The use of nontoxic excipients and sophisticated material engineering of lipid nanosystems allows for control of the physicochemical properties of the nanoparticles and improved GI permeation via mucosal or lymphatic transport.

Lipid-based nanodelivery systems, such as SEDDSs, nanoemulsions, microemulsions, SLNs, and NLCs, have great promise as oral vehicles for the delivery of bioactive agents because they can increase the solubility and improve bioavailability. Thus, many researchers have examined the effect of lipid nanocarriers on pharmacological or bioactive efficacy, adverse effects that are associated with conventional formulations and compliance by patients and consumers. Orally administered lipid nanoparticles can be absorbed by several different mechanisms (Figure 4).

When designing different formulations to improve the bioavailability of an oral vitamin, it is essential that the carrier stabilizes the vitamin and improves its transport into circulation. This chapter summarized recent advances in the use of vitamin-loaded lipid-based nanocarriers that were designed to enhance oral bioavailability. The selection of the carrier is important, and it should ideally provide maximal activity and minimal side effects. The use of lipid nanoparticles has numerous advantages over conventional formulations for dosing of vitamins, because they are more stable, they can provide sustained release, they can target different tissues, and they provide increased bioavailability. Some important limitations of conventional formulations, such as low solubility and poor epithelium permeation, can also be resolved by the use of lipid nanocarriers. Self-assembled lipid nanoparticles are frequently utilized to improve the oral delivery of vitamins. The type of emulsifier, particle size, interfacial composition, and vitamin concentration are the major factors that impact oral absorption. The comparison of different lipid-based nanoparticles used for enhancing oral vitamin delivery is summarized in table 2. Our introduction and description of the lipid-based nanocarriers that are used for vitamin delivery provide an overview for investigators who are attempting to design feasible and efficient delivery systems for vitamins and other bioactive agents. In the near future, it may be possible to extend the use of lipid nanoparticles by using them as vehicles for other functional nutrients.

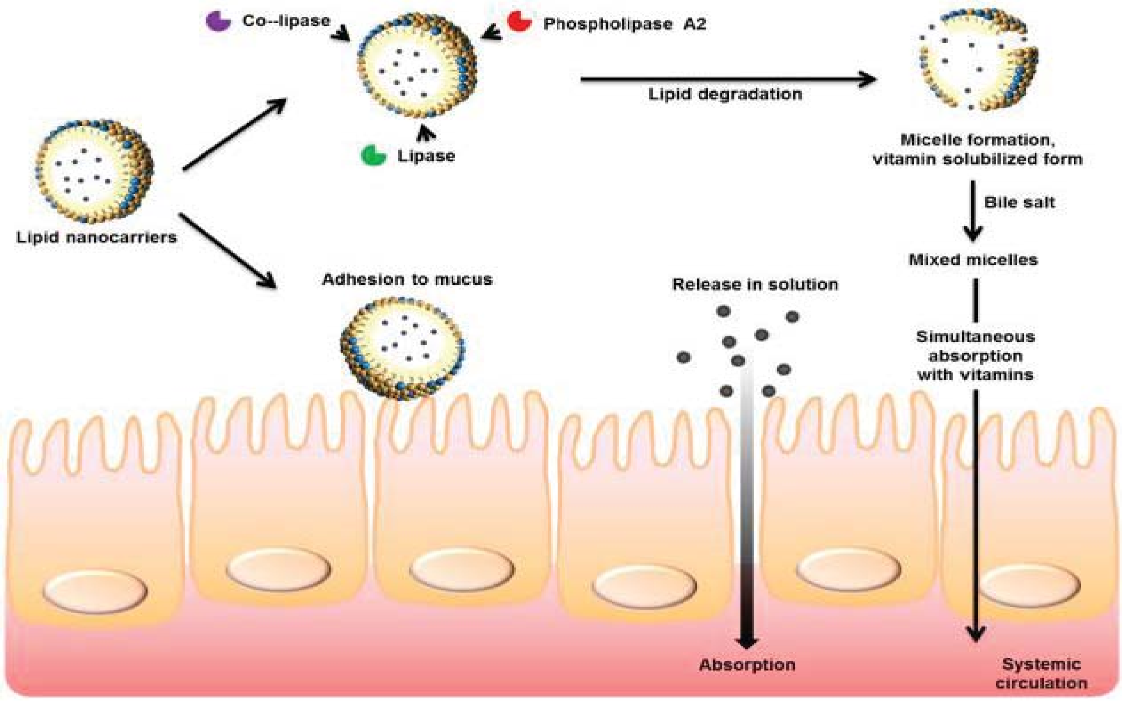

Figure 4 Possible pathways of gastrointestinal absorption of orally administered lipid nanoparticles.

Table 2: The comparison of different lipid nanocarriers for enhancing oral vitamin delivery.

Lipid Nanosystem	Nanoparticle Structure	Vitamins and Related Compounds Loaded
SEDDS	An anhydrous isotropic mixture of oil and emulsifier to spontaneously create nanoparticles in GI tract	Vitamin A, vitamin K1, vitamin K_2, coenzyme Q10, lutein, and tocotrienols
Nanoemulsions/ microemulsions	The isotropic or heterogeneous mixtures to form oil droplets in an aqueous system stabilized by emulsifiers	Carotenoids, vitamin D, vitamin D_2, and vitamin E
SLNs	The crystalline lipid structure in nanoparticles composed of melt-emulsfified lipids that are solid at room temperature	Astaxanthin and tocotrienols
NLCs	The second-generation lipid nanoparticles composed of a mixture of liquid and solid lipids for improving physical stability	Vitamin D_3

SEDDS: Self-Emulsifying Drug Delivery Systems; SLNs: Solid Lipid Nanoparticles; NLCs: Nanostructured Lipid Carriers; GI: Gastrointestinal.

Nanoformulations and substantiating the health benefits

Nanoformulations have been widely studied for the application of drug delivery. These involve the use of nanomaterials with sizes ranging between 1 and 100 nm. Due to their small size and large surface area, nanoparticle-incorporated compounds are superior in terms of their solubility, efficacy, safety, and pharmacokinetics [82]. The application of nanoformulations for the delivery of lipophilic drugs and/or active compounds offers several benefits, including protection from gastrointestinal degradation, prolonged systemic circulation, controlled drug release and improved absorption in the intestine [83]. These in turn improve the bioavailability and enhance the efficacy of administered drugs or active pharmaceutical compounds.

To overcome the poor bioavailability of vitamin E, different nanoformulation strategies have been used to address the issue for potential therapeutic applications [84]. These strategies include loading vitamin E in nanovesicles, Solid-Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs), nanoemulsions and polymeric nanoparticles (Figure 5).

Noting the absence of a shared definition of nutraceuticals, scholars have recently argued that 'the effective use of nutraceuticals in prevention and therapy' is limited by 'the lack of clinical data substantiating in full their efficacy which prevents the obtainment and use on the label of a health claim [85,86]. The industry, however, is aware of the need to support and promote an evidence-based approach.

Nutraceutical manufacturers formulate both self-produced and contracted ingredients. Whereas the pharmaceutical industry mostly relies on active pharmaceutical ingredients purchased by fine chemical and Active Pharmaceutical Ingredient (API) manufacturers, mostly located in Asia (the 'contract manufacturing organizations'), the nutraceutical industry tends to partner with a few suppliers acting more as co-manufacturers rather than suppliers needing to undergo regular audits and certification.

Both ingredient manufacturers and finished nutraceutical manufacturers are part of the very same industry, in which synergy dominates and the success of all business partners is a common interest of the partnerships characterizing the industry.

Organic chemists working in other organic process industries may find it instructive to learn how the nutraceutical industry has developed some of its advanced technologies, often in partnership with small companies, focusing on specific nutraceutical ingredients whose efficacy was recognized by regulatory authorities. Selected examples show evidence of this trend.

CONCLUSION

Foods are nanostructured materials composed of hundreds of thousands of nanosized particles and molecules assembled in characteristic forms of the living organism. However, these arrangements are not considered within the nanofield unless the isolated materials and particles perform independently as nanomaterials by exhibiting characteristic properties that do not possess at the microscale. Current legislation states that FDA-regulated nanoproducts should meet the requirement to possess at least one dimension in the nanoscale range that allows the product to exhibit properties or phenomena, including physical or chemical properties or

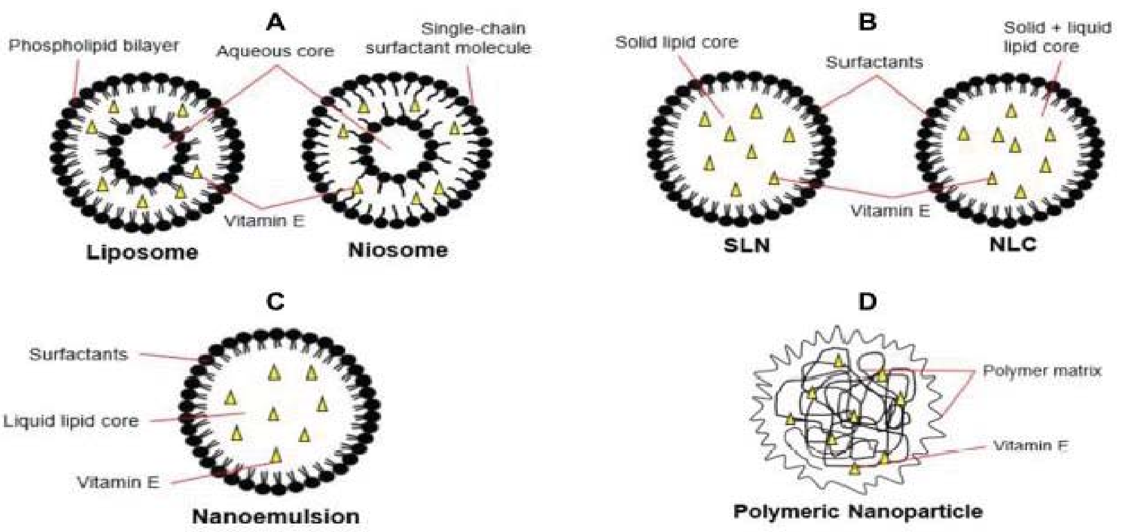

Figure 5 Schematics for different vitamin E nanoformulation strategies. (A) Liposomes and niosomes (B) Solid-Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs); (C) Nanoemulsions and (D) Polymeric Nanoparticles.

biological effects, attributable to its Nanodimension(s). A comprehensive report on this matter, including an extensive guide to industry can be Found Online (FDA) [87].

Nanostructured Lipid Carriers (NLCs) composed of solid lipid and oil are a new generation of lipid nanoparticles which have exhibited some merits over traditional used lipid nanoparticles in fortifying food and beverages and nutraceuticals delivery systems such as liposomes and solid lipid nanoparticles. Many recent advances in nutraceutical science and technology – from the new green chemistry processes mentioned above to the new role of phytochemistry in the emerging bioeconomy – are ideally suited to enter the curricula of renewed chemistry courses using recent research outcomes [88]. Both SLNs and NLCs remained unchanged after an in vitro stomach digestion assay, which allows delivery in the intestine where lipid digestion occurs, possibly allowing the release of Vit A for its absorption. The Vit A delivery system has been the potential for application in functional foods or beverages [89]. The Vit A was successfully encapsulated in lipid nanoparticles (SLNs and NLCs) using an organic solvent-free sonication method, towards food fortification. The optimal nanoparticles were obtained by evaluating the effects of solid and liquid lipids in their composition. The optimized formulation of SLNs was obtained with Gelucire® 43/01 and the NLCs with Gelucire®43/01 and miglyol® 812, supplemented with α-tocopherol. The DLS data and TEM images collectively suggested spherical nanoparticles in monodisperse populations. When stored at room temperature, in aqueous suspension, up to a month, NPs retained their initial properties. The optimized NPs were also stable to heat treatments of up to 70°C for periods of 15 min and in different media simulating several conditions of food products. The fibroblasts studies revealed the non-cytotoxicity of the formulations. Yet, there is still much to be explored to unravel the mechanism of absorption and to evaluate the performance of this system under in vivo conditions using animal or human feeding studies. Likewise, the impact of these nanoparticle delivery systems on the quality and stability of real food products should be established, including the evaluation of the effect of this supplementation on the sensory properties of food products.

It was concluded that Nanostructured Lipid Carriers (NLCs) showed a promising approach for fortifying beverages by lipophilic nutraceuticals such as vitamin D. At last, it can be concluded that by the novel developed technique and the optimized chitosan coverage, very stable and mucoadhesive polymer–lipid hybrid nanoparticles, encapsulating vitamin D3 and vitamin K2, are produced as micronutrients delivery systems for potential nutraceutical applications. In vitro and in vivo studies have demonstrated that nanoformulations improve the delivery and efficacy of vitamin E by enhancing its absorption, cellular uptake, solubility, and stability. These promising findings suggest that nanoformulations should be applied as carriers of vitamin E, particularly tocotrienols, to achieve better therapeutic applications.

Future developments include [90,91] processed nanostructured or textured food (less use of fat and emulsifiers, better taste); nanocarrier systems for delivery of nutrients and supplements in the form of liposomes or biopolymer-based nanoencapsulated substances; organic nanosized additives for food, supplements and animal feed; inorganic nanosized additives for food, health food, and animal feed; and food packaging applications such as plastic polymers containing or coated with nanomaterials for improved mechanical or functional properties, nanocoatings on food contact surfaces for barrier or antimicrobial properties, surface-functionalized nanomaterials, nanosized agrochemicals, nanosensors for food labeling, water decontamination and animal feed applications such as nanosized additives that can bind and remove toxins or pathogens

Finally, the global nutraceutical industry has experienced dramatic growth. Revenue of $231 billion in 2018 is projected to grow at a 7.8% compound annual growth rate from 2018 to 2023 [85]. The growth of Italy's nutraceuticals market, currently the largest in Europe, accompanied that of the rest of the world. As the global shortage of highly skilled workers, universities will find in nutraceutical science and technology a key area of the unfolding bioeconomy through which to expand and to improve their educational programs.

In summary, this chapter supplies a new strategy for the nanostructures and nanoencapsulation of vitamins -minerals and motivates its application in food products supplementation.

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