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# Nanoformulated Delivery Systems of Essential Nutraceuticals and Their Applications

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## Abstract

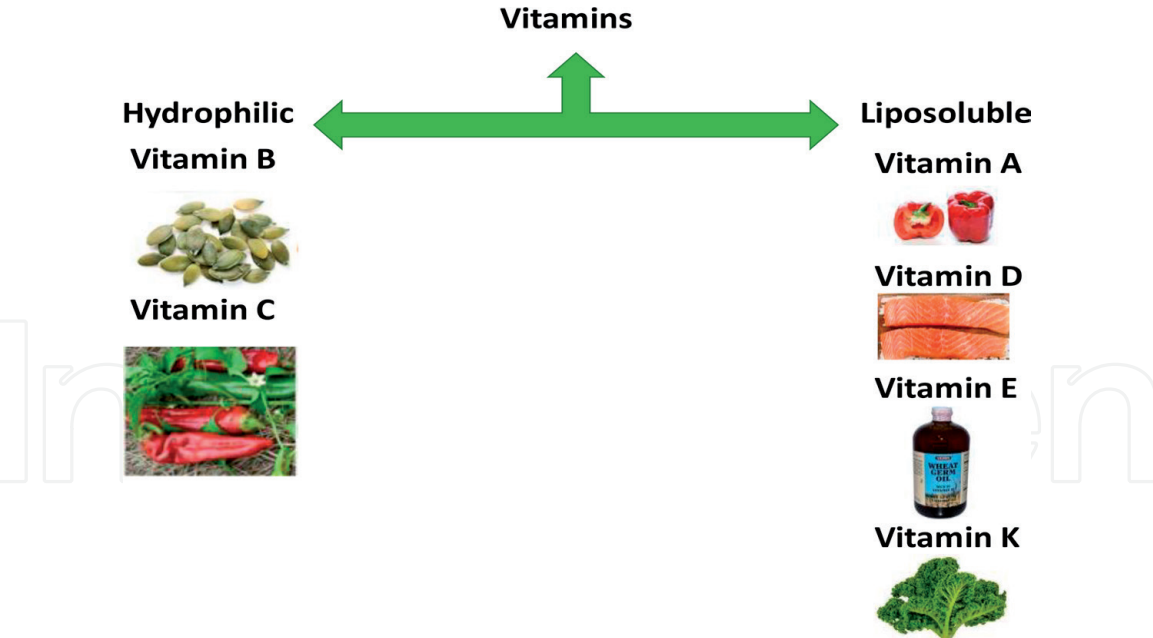
Malnutrition and poor diet constitute the number one driver of the global burden of disease. Undernutrition is responsible for up to 50% of all deaths in children under the age of 5. In South Africa, 25% of the country's children suffer from undernutrition. This increases the risk of child mortality as well as contracting infectious diseases. It also affects the physical and intellectual development of the children. The greatest drawback in malnutrition is the deficiency of essential nutraceuticals involved in important biological functions. Innovative technologies such as nanoformulated products are needed for food and agriculture in order to enhance the children's health. The evaluation and application of various nanoformulated delivery systems will be explored for improving the stability and bioavailability of essential nutraceuticals for consumers.

**Keywords:** nanoformulated, nutraceuticals, delivery systems, undernutrition, food, agriculture

## 1. Introduction

Over the past years, nutraceuticals have been explored as novel medicinal dietary products in the food and pharmaceutical industries. Dr. Stephen De Felice invented “nutraceutical” as a term in an attempt to promote medical health research [1–2]. He defined it as a food or part of a food that provides medical or health benefits, including the prevention and treatment of disease. Nutraceuticals are mostly classified into three broad groups such as dietary supplements (glucosamine, probiotics, etc.), herbals (herbs or botanical products), and nutrients (vitamins, minerals, etc.). In addition, they are consumed daily by human beings as an alternative to modern medicine, thus promoting quality life and increasing life expectancy. They have proved to offer benefits such as acting as a natural antioxidant and immune booster, fewer side effects than drugs, improved bioavailability, and long half-life [3]. The focus of the chapter will be limited to various sources of vitamins especially nanoformulated liposoluble vitamins.

Great progress toward enhancing the stability and bioavailability of vitamins, thus promoting health benefits among consumers, has been achieved by various researchers [4–6]. **Figure 1** shows a classification of vitamins according to their solubility. In the last decade, an extensive amount of research has focused on the



**Figure 1.**  
*Classification of vitamins with some examples of high rich foods.*

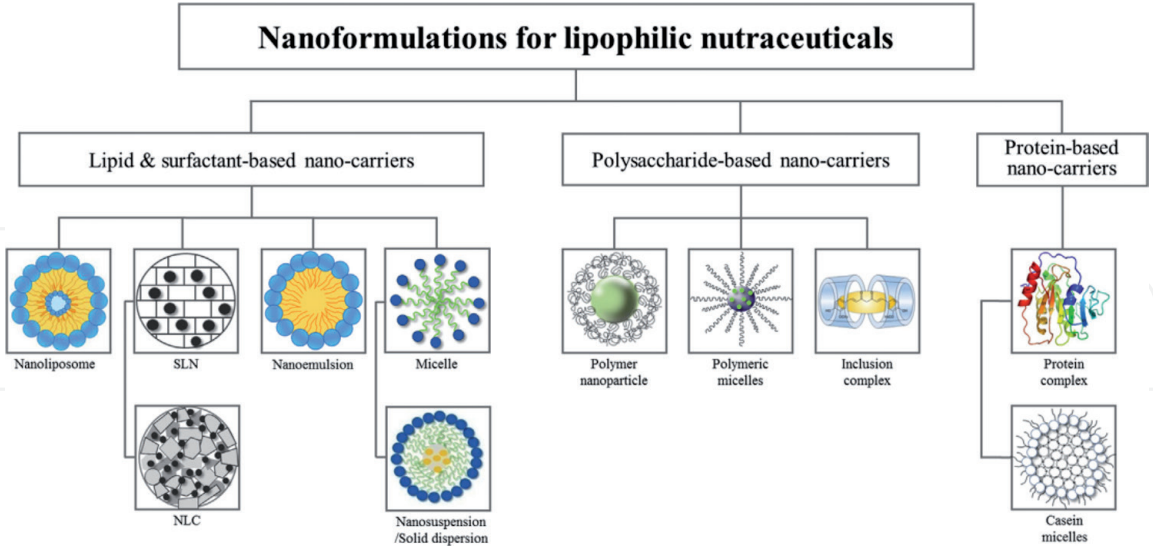
hydrophilic vitamins as compared to liposoluble ones [7, 8]. Different approaches have been explored to improve the stability and functionality of hydrophilic vitamins during product development and storage of food because of the exposure to high temperature, oxygen, and light. Novel methods were used by Alishahi et al. [9] to increase the shelf life and delivery of vitamin C using chitosan nanoparticles. In addition, three different vitamins (B9, B12, and C) were successfully encapsulated in water-soluble derivatives of chitosan biopolymer [10]. Their study showed that N,N,N-trimethyl chitosan nanoparticles can successfully be used as a stable vitamin carrier system with potential applications in foodstuffs.

**Table 1** highlights some of their health benefits and disease prevention [11–13]. Many of these vitamins have been found to have major limitations such as low chemical stability, sensitive to oxidation, high melting points, and poor solubility, thus leading to low bioavailability [14]. The inability of the human body to produce vitamins forces humans to have a balanced diet in order to intake the recommended supply of essential nutrients. The inadequate intake of various vitamins through diet may compromise biological functions such as vision, growth and development, immunological activity, reproduction, and cellular growth [11]. The application of adequate treatment can reduce the risk of development of complications related to deficiency of vitamins. Food fortification and supplements have been used as strategies to prevent vitamin deficiency. In order for nutritional supplement premixes and fortified food to work, the vitamins and micronutrients contained in these products need to remain active until consumption, which may not always be the case. Premixes and fortified foods may lose a large percentage of vitamins and micronutrient activity before consumption via processing, packaging, transportation, and storage. Therefore there is an urgent need to develop and explore cost-effective innovative approaches that will improve the stability of nutraceuticals especially liposoluble vitamins.

The delivery of vitamins using nanotechnology has attracted a number of attention recently [14] and is proposed as one of the possible innovative approaches. Numerous methods including spray-drying, spray-cooling, phase separation, emulsion systems, liposome solid lipid nanoparticles (SLN), and inclusion complexation have been proposed for the nanoformulations of liposoluble vitamins as depicted in **Figure 2**. Some of the methods including nanoemulsions, polymeric and lipid nanoparticles, etc. will be discussed in the chapter.

Vitamin, chemical name	Recommended daily intake	Health benefits	Deficiency
Vitamin A, retinol	300 µg (1–3 years), 400 µg (>4 years)	Antioxidant, improves vision and bone growth, regulates cell proliferation, treatment of skin cancer and leukemia	Xerophthalmia caused by unbalanced diet or malabsorption diseases, liver disorders, night blindness
Vitamin D, cholecalciferol	5 µg (4–8 years)	Essential for healthy bones, controls the amount of calcium in the blood	Growth slowed in children, inadequate diet, inadequate exposure to sunlight, severe deficiency leads to rickets, osteomalacia, muscle pain, severe asthma in kids
Vitamin E, tocopherol	6 mg (1–3 years), 7 mg (4–8 years)	Strengthens body's immune system, keeps blood vessels clear and flowing well, boosts the immune system, healthy skin and eyes, antioxidant	Deficiency might lead to premature infants
Vitamin K, phyloquinone	30 µg (1–3 years), 55 µg (4–8 years)	Essential for blood clotting and blood coagulation	Subdermal hemorrhaging, deficiency leads to uncontrolled bleeding and clotting

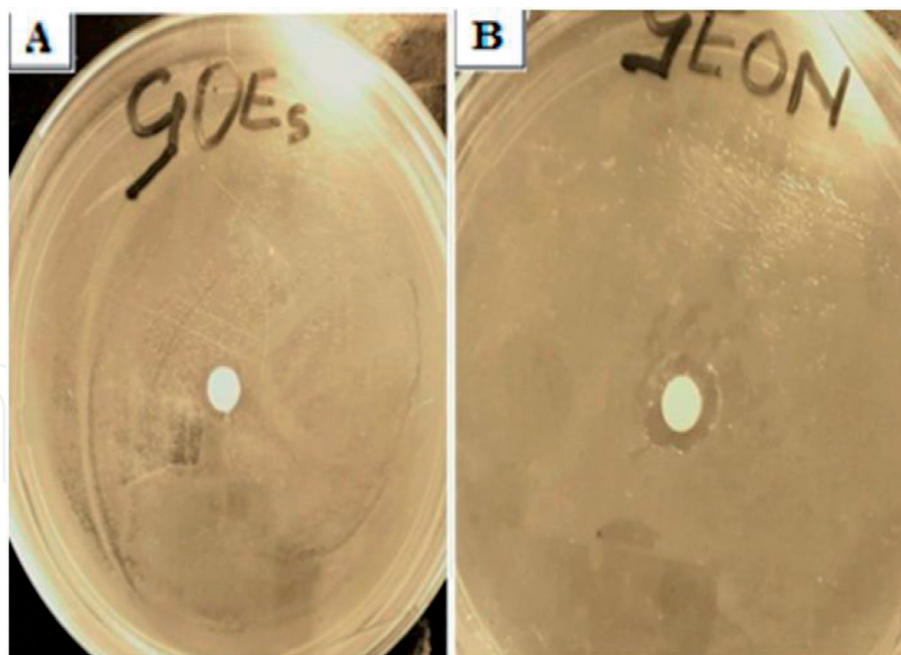
**Table 1.**  
*Recommended daily intake, Health benefits, and deficiency of liposoluble vitamins [11–13].*



**Figure 2.**  
*Nanoformulations for liposoluble vitamins [14].*

1.1 Nanoemulsions

Colloidal dispersions consisting of oil droplets dispersed in an aqueous medium in the 5–200 nm range are known as a nanoemulsion. They are isotropic systems, which are kinetically stable compared to conventional emulsions. Furthermore, they are transparent or translucent to the naked eye [15]. They have also been found to hold special characteristics such as protection from oxidant and hydrolysis in oil-in-water



**Figure 3.** Photographic evidence of the antimicrobial inhibition of (A) garlic essential oil and (B) garlic essential oil nanoemulsions [19].

(O/W) nanoemulsions [16], encapsulation of hydrophilic drugs [17], enhanced bioavailability of drugs [18], and increased antimicrobial activity of essential oil [19]. **Figure 3** shows an enhanced inhibition level against *Escherichia coli* of garlic essential oil nanoemulsions (GEON) as compared to garlic essential oil [19]. The study by Katata-Seru et al. further revealed an easy and effective Taguchi method for optimizing GEON and as a potential alternative to antimicrobial broiler growth promoters.

There are various types of nanoemulsions and the most common ones are O/W type, water-in-oil (W/O) type, and bi-continuous type, for example, water-in-oil-in-water (W/O/W) type. A number of different preparation techniques for nanoemulsions have been investigated intensively using low and high energy. Low energy includes spontaneous emulsification and phase inversion temperature, while high-energy such as microfluidics, high-pressure homogenizers, or ultrasound equipment methods are used. The food-grade nanoemulsions have generated a huge interest using processing operations such as homogenization and mixing and shearing and homogenization [7, 20]. Recently, Öztürk evaluated various studies on enhanced bioavailability of vitamins A, D, and E encapsulated in O/W nanoemulsions and their factors affecting their stability [16]. Emulsion systems for encapsulation of vitamin E showed that nanoemulsion formulation improved the emulsion stability with an average particle size of 277 nm when compared to the standard emulsion [20]. Although it appears that significant research on nanoemulsions is on the rise, Öztürk highlighted a need for more in vivo bioavailability studies of the foods fortified with lipophilic vitamins as their studies are few owing to the higher costs.

## 1.2 Polymeric nanoparticles

Polymeric nanoparticles (NPs) are solid carriers capable to adsorb, disperse, entrap, and attach active ingredients to its matrices with the size of smaller than 1  $\mu\text{m}$ . They are produced from preformed polymers by emulsion solvent evaporation, salting out, dialysis, nanoprecipitation, and supercritical fluid (SCF) technology. The NPs have displayed fairly good stability, higher loading efficiency, and controlled release of bioactive compounds as compared to emulsion, micelles, and



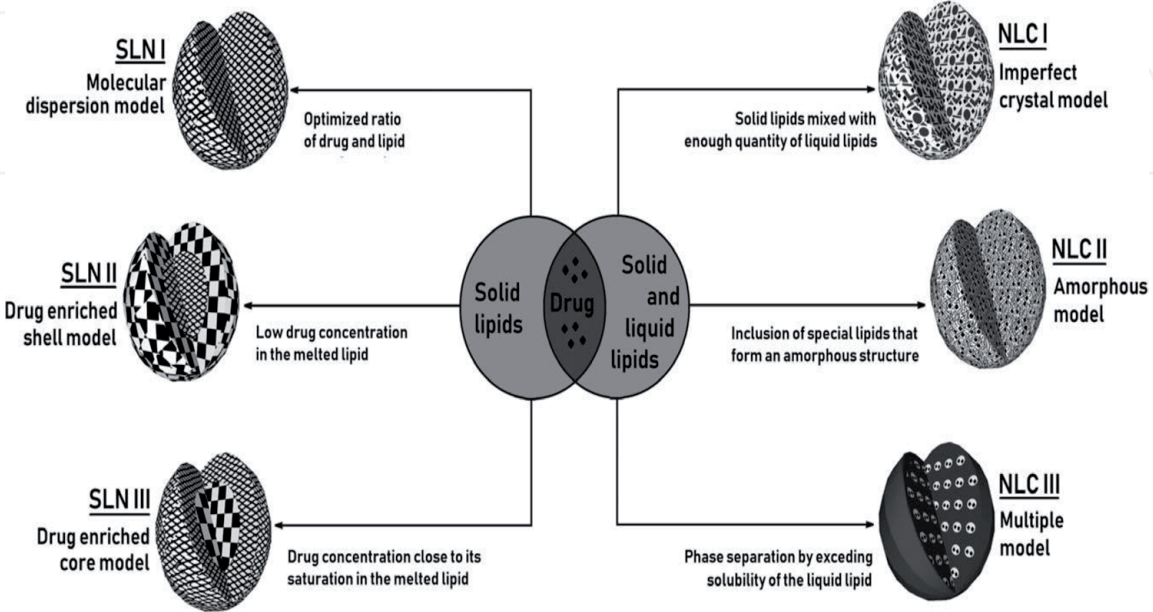
liposomes [14]. In addition, they have been studied extensively in the nutraceutical field because of characteristics including increased stability, the capability to protect drugs, etc. [21, 22].

Studies have fabricated a unique polymeric vitamin E-modified aliphatic polycarbonate (mPEG-PCC-VE) to assist oral absorption of oleanolic acid (OA) [23]. The OA demonstrated excellent pharmacological activities in the clinical treatment of hypoglycemia, immune regulation, acute jaundice, and chronic toxic hepatitis. In spite of this, OA has limited water solubility and poor intestinal mucosa permeability when delivered orally. The results of OA encapsulated mPEG-PCC-VE NPs illustrated homogeneous 170 nm particle size with a drug loading of 8.9% and a potential platform to facilitate the oral delivery of OA.

### 1.3 Lipid nanoparticles

Lipid nanoparticles were developed as an alternative to traditional nano-systems such as polymeric particles and liposomes. Lipid nanoparticles can be defined as colloidal particles composed of lipids stabilized by surfactants that are solid at ambient temperature with sizes varying between 40 and 1000 nm [24, 25]. The first lipid nanoparticle to be produced was solid lipid nanoparticles as depicted in **Figure 4**. SLN is made from solid lipid only. The second generation of lipid nanoparticles was developed a few years later called nanostructured lipid nanoparticles (NLC). NLC is made from a blend of solid and liquid (oil) lipids [26]. The addition of oil in NLC formulation is meant to distort the formation of perfectly structured lipid crystals found in SLN, thus creating more room with uptake capacity for the encapsulated active. This was first shown by Jennings and Gohla, when they increased the loading capacity of retinol (vitamin A) from 1 to 5% by using NLC [27].

Lipid particles can be produced using various methods such as high-pressure homogenization, microemulsion, emulsion solvent evaporation, emulsification-solvent diffusion, solvent displacement, phase inversion, ultrasonication, and membrane contractor technique [24]. However, of these techniques, only a few have been applied to prepare lipid nanoparticles with vitamins. Vitamins are sensitive



**Figure 4.** Models for the structure solid lipid nanoparticles and nanostructured lipid carriers that can be obtained under different conditions determined by the nature of the components and their relative solubility [25].

bioactives, and thus care should be taken to employ techniques that will retain their activity during formulation. The most widely used techniques to prepare lipid nanoparticles with vitamins are the emulsion solvent evaporation method, high-pressure homogenization, and microemulsions.

### *1.3.1 Emulsion solvent evaporation method*

This method is based on the dispersion of a solution of the lipid components in an aqueous surfactant solution. The lipids and the lipophilic bioactive are commonly dissolved in an organic solvent such as dichloromethane, cyclohexane, ethyl acetate, or chloroform. When the nanoemulsion is formed, the solvent is extracted or evaporated, and the droplets start to solidify until solid lipid nanoparticles encompassing the active are formed. The solvent can be evaporated by agitation, rotary evaporation, or spray-drying [28]. The emulsion solvent evaporation method offers a great advantage for encapsulating actives that are highly sensitive to heat such as vitamins as no thermal stress is needed [29].

### *1.3.2 High-pressure homogenization*

This technique involves the preparation of a pre-emulsion, which is then passed under high pressure (100–2000 bar) through a homogenizer valve. The pre-emulsion generally composes a lipid phase and an aqueous phase containing a surfactant. The fluid is accelerated in a very short distance in the homogenizer, reaching a high speed. The lipid substances are then divided into small droplets by the shear stress forces. This technique may produce particles with low encapsulation efficiency for hydrophilic substances due to the drug migrating to the external aqueous phase during particle formation. However, lipophilic actives can be encapsulated at high dosage [30, 31]. The technique is also ideal for the production of large quantities of sterile particles, which is an advantage for nutraceuticals [26].

### *1.3.3 Microemulsions*

Microemulsions are clear, thermodynamically stable, and isotropic liquid mixtures of oil, water, and surfactant and almost always co-surfactant as well. The droplet size in the dispersed phase of the microemulsion is less than 100 nm. The droplets are formed by the drastic cooling of a microemulsion mixture to solidify the droplets and create particles loaded with the bioactive. The preparation of microemulsions does not require much energy to form and is thus recommended for actives that are highly sensitive to shear forces or thermal stress as is the case with most vitamins [29]. Other advantages of microemulsions include the use of bioactive compatible ingredients and the enhanced stability of formulations, as they are thermodynamically stable [32].

After preparation, lipid nanoparticles can be stored as nanosuspensions in the medium they were formed, or dry particles can be obtained using either freeze-drying or spray-drying [25]. In some instances, aggregation of particles may occur due to the drying process. In these instances, an adequate amount of cryoprotectant can be added to prevent or minimize aggregation of the particles [30].

### *1.3.4 Lipid nanoparticles for the delivery of vitamins*

There has been an increasing awareness of maintaining personal health by balanced nutrition and the intake of nutraceutical supplements. Due to the challenges faced with the stability of nutraceuticals, lipid formulations have been sought to

enhance the stability of these bioactives. Lipid nanoparticles are highly recommended for the delivery of vitamins firstly due to their physical stability, secondly due to their ability to protect actives from environmental factors such as oxidation, hydrolysis, and possibly enzymatic degradation in the gastrointestinal tract, and thirdly due to their cost-effective production at large scale, for example, high-pressure homogenization.

Following the study by Jennings and Gohla, liposoluble vitamins A, D, E, and K as well as their derivatives have been presented as good candidates for encapsulation using lipid systems due to their low bioavailability and relative instability [33]. With the aim of increasing the intestinal absorption of vitamin K, vitamin K1 was encapsulated in SLN and demonstrated stability for more than 2 days in simulated gastric and intestinal fluids. The encapsulation also increased storage stability of vitamin K1 up to 4 months at 25°C [34]. Vitamin A in the form of all trans-retinol suffers degradation reactions that are characteristic of conjugated double bonds resulting in loss of its bioactivity. The vitamin was encapsulated in SLN and demonstrated an enhancement of retinol stability, photostability, and preservation of its antioxidant activity [35]. The lipophilicity, chemical instability, and poor skin penetration of vitamin E have limited its effectiveness as an antioxidant and photoprotectant used in various pharmaceutical and cosmetic products [25]. Various lipid formulations with vitamin E were developed, and the results obtained showed the possibility to enhance chemical stability and physical stability of Vitamin E in a cream [36]. In other formulations, Tween 80 was mixed with various lipids and surfactants to produce particles with the ability to protect vitamin E against photodegradation [37, 38]. Ying and Misran produced a thermoresponsive gel for topical application that could control the release of vitamin E [39].

#### **1.4 Polymeric micelles**

Polymeric micelles are formed from block copolymers that have amphiphilic character. Amphiphilic polymers are copolymers composed of hydrophilic (“water-loving”) and hydrophobic (“water-hating”) parts [40]. They normally form spontaneously under certain concentrations and temperatures in a given media [41]. The concentration at which these micelles are formed is known as critical micelle concentration (CMC), while the temperature at which this micelle exists is called the critical micellization temperature (CMT) [41]. Hydrophobic blocks of amphiphilic polymers form the core of the micelle, while the hydrophilic blocks form the shell [42, 43]. They can be utilized as drug carriers, by incorporating the poorly soluble nonpolar substances within the micellar core and polar substances on the micellar shell (by adsorption); substances with intermediate polarity are distributed between the core and shell [41, 44]. These properties enable these systems to incorporate poorly water-soluble drugs in the micellar core by physical interaction or by chemical conjugation leading to higher solubility extents [43], to protect the drugs or sensitive substances from premature degradation and also reduce the toxicity of the drug [42]. When compared to conventional micelles, polymeric micelles have lower CMCs values and are more stable even at concentrations below CMC [41]. This behavior stems from the slower rate of dissociation that depends on the molecular weight and hydrophilic-hydrophobic balance of the polymer as well as the properties of the drug incorporated into the core [43].

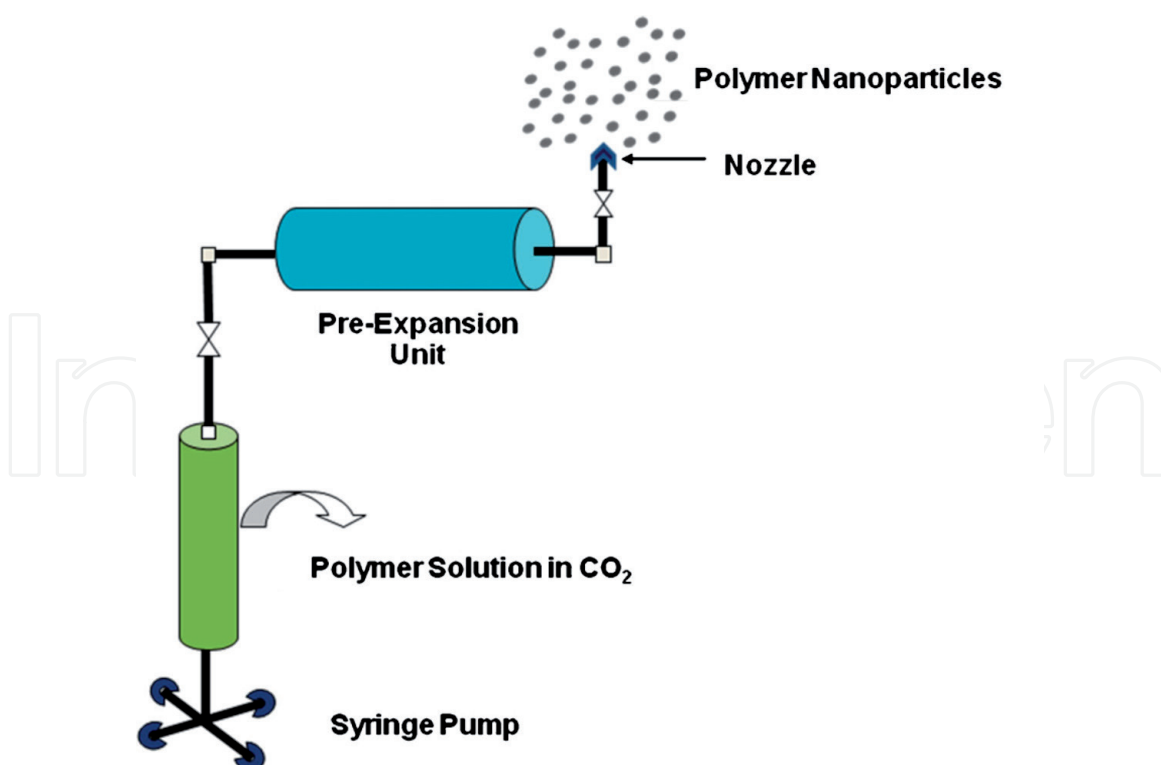
#### **1.5 Supercritical fluid technology**

The methods discussed in the preceding sections involve the use of organic solvents, which could impart residual moisture of organic solvents on the produced nanoparticles. Supercritical fluid technology, on the other hand, utilizes the CO<sub>2</sub>, which often



produces nanoparticles or microparticles without any trace of solvent, thus high purity.  $\text{CO}_2$  is a cheaper fluid, nontoxic, and non-flammable. Its low critical temperature of  $31.1^\circ\text{C}$  makes it an ideal fluid for sensitive or thermally labile materials. An active ingredient is regarded to be in a supercritical state if its temperature and pressure are above its critical values. Based on the solubility of active ingredient in  $\text{CO}_2$  (or any inert gas) fluid, particles can be formed by using two approaches as depicted in **Figure 5**: (a) rapid expansion of supercritical solution (RESS) and (b) rapid expansion of supercritical solution into a liquid solvent (RESOLV) [45]. In order to perform RESS, high solubility in the supercritical fluid is required. However, some of the active nutraceutical ingredients are organic polar compounds.  $\text{CO}_2$ , due to its low polarity, is not a proper fluid for these materials. The nutraceutical ingredients are ideal for RESOLV. In RESOLV, an organic solvent is required to dissolve the vitamins expanding in the SCF.

As discussed in Section 2.3, solid lipid nanoparticles are spherical nanoparticles produced from solid fat. Instead of melting the lipids in an appropriate organic solvent, vitamin B2 was encapsulated in SNL using SCF [46]. The lipids are saturated with  $\text{CO}_2$  in order to decrease the melting point. However, Couto and colleagues modified the SCF, in which the lipid, bioactive, and surfactant mix expanded with  $\text{CO}_2$  was decompressed into a water stream containing a stabilizer. Vitamin B2, the hydrophilic bioactive, was encapsulated in fully hydrogenated canola oil (the solid lipid), using sodium lauryl sulfate as surfactant and polyethylene glycol as stabilizer. Vitamin B2 participates in a range of redox reactions central to human metabolism, and its deficiency has been linked to fetal developmental abnormalities and deficiencies in the production of red blood cells. Due to its hydrophilic nature, it is easily absorbed, but it is not stored in the body, leading to the need for



**Figure 5.**

*A Schematic representation of particle formation by rapid expansion of supercritical solution. In conventional RESS, blank particles are formed dissolving the solute, that is, polymer in a supercritical fluid to form a solution. This is followed by the rapid expansion of the solution across an orifice or a capillary nozzle into ambient air. The high degree of supersaturation, accompanied by the rapid pressure reduction in the expansion unit, ideally results in homogenous growth of particles and, thereby, the formation of well-dispersed particles. However, results obtained from mechanistic studies of different model solutes for the RESS process indicate that both nanometer- and micrometer-sized particles are usually present in the expansion unit [46].*

replenishing its levels every day. By encapsulating it in SLN, it is anticipated that a sustained release can be obtained and its absorption can be slowed down.

## 2. Conclusions

Numerous delivery systems such as nanoemulsions, microemulsions, liposomes, lipid nanoparticles, polymeric micelles, and nanoparticles have been reported extensively for encapsulating nutraceuticals especially liposoluble vitamins. The lipid-based nanoformulations were highly recommended by various studies as compared to others due to their better absorption when ingested, improved stability, and low degradation in the gastrointestinal tract. However, more efforts need to be focused on their toxicity and regulatory issues for the faster development of industrially processed nanoformulated nutraceuticals from the lab-scale research discoveries. It is widely anticipated that over the next couple of years, nanoformulated delivery systems of essential nutraceuticals will continue to evolve and many novel food products are expected to be used with an enormous positive impact on addressing malnutrition challenges in children.

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