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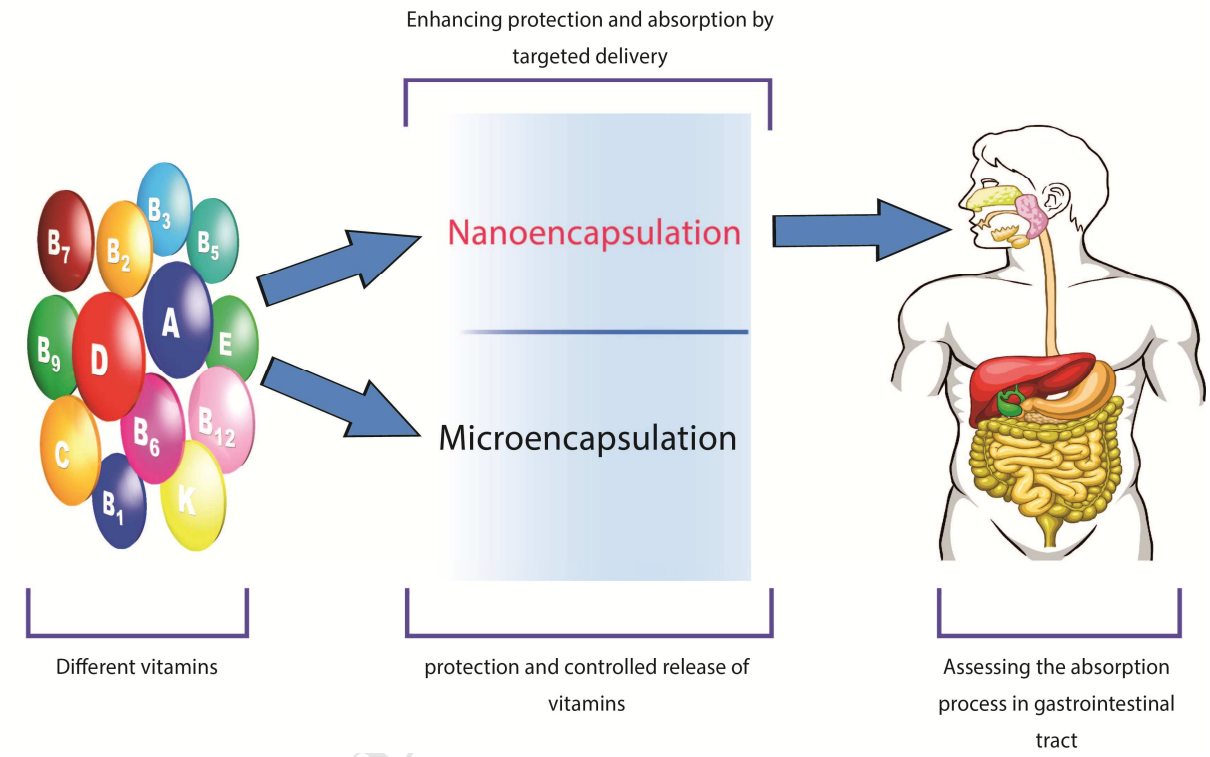
Graphical Abstract



Nano-encapsulation as a promising approach for targeted delivery and controlled release of vitamins

Running Title: Nano-encapsulation of vitamins

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Structural abstract

Background

Vitamins are bioactive molecules necessary for human health, which are sensible to degradation. During consumption, the bioavailability of these compounds might be limited due to structure break-down and low absorption. Today, nanoencapsulation can be a promising approach for targeted delivery of vitamins and protecting these bioactive components against destructive environment during processing and delivery. Regarding the benefits of utilizing nanotechnology in the food sector, safety aspects of these tiny carriers should also be clarified as this technology develops. Due to the possible negative effects of nanomaterials, several agencies have legislated regulatory policies to prevent potential harms to the consumers, which are underlined in this article.

Scope and approach

Nanoencapsulation-based technologies are a unique and novel field of investigation in the food and pharmaceutical industry with benefits, such as higher bioavailability, high shelf-stability and controlled release of active compounds. This review highlights recent works on these techniques and advances made in nanoencapsulation of lipophilic and hydrophilic vitamins, safety issues and health risks regarding the consumption of these products, which opens new horizons in food technology and nutrition with possibilities of commercialization in the near future.

Key findings and conclusions

Recently, considerable progresses are being carried out in the field of food nanoencapsulation involving novel nanovehicles to encapsulate vitamins. Nanofibers and nanohydrogels are some examples of efficient and modern nanocarriers. Overall, the vitamins encapsulated within nanovehicles are considered safe since they are mostly produced from food components, meanwhile more studies should be performed regarding the safety issues of nanodelivery of vitamins. In near future, it is assumed that nanoencapsulated vitamins will be broadly applied the in the food and beverage products.

Keywords: Nanoencapsulation; vitamins; food industry; safety; bioavailability.

1. Introduction

Vitamins and antioxidants are rudimentary elements for human health as they assist the body to grow and develop. Furthermore, they are able to prevent diseases and to promote general health. Unfortunately, most of these bioactive agents are either produced in trifle amounts or not made in the body. Thus, vitamins need to be supplied from food products and through dietary supplements if needed (Wildman, Wildman, & Wallace, 2006). Some of the beneficial functions of vitamins are as follows: enhancing the immune system and vision, supporting skin health and cell growth and helping to prevent cancer (vitamin A); empowering the immune system, alleviate anxiety and depression, reduce stroke risk and relieve PMS (premenstrual syndrome) (vitamin B-complex); raising immunity, treating common cold symptoms, maintaining healthy skin, healing wounds, reducing cholesterol levels and regulating the blood sugar level, reducing neurological disorders (vitamin C)(Hickey, 2009), preventing cancer and cardiovascular diseases as well as promoting vigorous bones and teeth (vitamin D), restraining brain and nervous system diseases; such as, Alzheimer and other dementias, boosting physical endurance and avoiding skin disorders (vitamin E), helping blood clot, nerve signaling, improving bone health and regulating cellular functions (Zempleni, Suttie, Gregory III, & Stover, 2013).

Vitamins are sensitive molecules; therefore they should be preserved from harmful agents like heat and oxidants. Encapsulation is a promising and novel method for preserving the innate characteristics of vitamins over time (Sanguansri & Augustin, 2006). This process includes coating or trapping a biomaterial or a combination into another element. The entrapped substance is normally a liquid, while a gas or solid state substance can also be carried. The coating substance is known as capsule, wall material, membrane, or carrier.

Our body has nanoscale structures like DNA, amino acids, etc. (Weiss, Takhistov, & McClements, 2006). Considering these natural nanoparticles, scientists have engineered nanomaterials for the usage in human's food and recently, there has been a tremendous progress in food nanoencapsulation.

In this study, after a brief review on pros and cons of food nanotechnology and microencapsulation of vitamins, we will highlight recent fundamental and novel techniques used to nanoencapsulate different vitamins in the food industry. Besides, issues on the characterization, controlled release and safety-consumption of these vital elements are described. Future trends will also be explained in the last section.

2. Pros and cons of applying nanotechnology in the food industry

Today, the entry of nanotechnology within the food sector has brought new hopes and is expected to be the key to food industry's concerns as it may bring various benefits, nevertheless like the other emerging technologies it could also have risks for consumers. According to Aguilera (cited in Yaktine & Pray, 2009), exerting nanotechnology in food industry may bring about various advantages and opportunities; such as, developing promising nano-processes, fabricating eco-friendly processes and intelligent nano-packaging, manufacturing products with desirable texture and tastes, producing low-calorie food and beverage products

with the aim of changing the lifestyles into healthy ones. He also suggested that there are still more opportunities which will be accomplished by carefully studying how food components are formed, disintegrated, ingested and absorbed and without this perception it wouldn't be possible to overcome the potential risks and uncertainties within this technology.

Regarding the risks and disadvantages of applying nanotechnology in food industry, most of the nanoparticles enter the gut through oral administration and absorption via intestine cells (enterocytes) is designed in a way that they do not allow large or foreign particles to pass through them, nevertheless the nano-sized ingredients are able to cross these barriers, therefore there is a potential risk in bringing up gastric diseases which should investigated through *in vivo* and clinical studies.

3. Microencapsulation vs. nanoencapsulation of vitamins

Micro/nanoencapsulation is defined as the creation of a barrier to inhibit unfavorable chemical interactions and for the controlled release of bioactive ingredients especially vitamins. Importance of using the microencapsulation processes for vitamins and their key features could be summarized as below:

- Protection of vitamins from external environment
- Controlled release of vitamins
- Improved flow properties
- Reduce overages
- Measuring the precise level of vitamin delivery
- Forming Light-scattering vitamin solutions
- Being cost effective especially for spray drying method
- Undesirable flavor of some vitamins are masked
- Enriching the food products with a complex of vitamins

While for nano-encapsulation of vitamins, the following advantages can be mentioned:

- ✓ Faster dissociation
- ✓ Higher surface area compared to mass proportion
- ✓ High intracellular uptake
- ✓ Pass along the smallest body fenestrations
- ✓ Enable precision targeting
- ✓ Reduce the reactions between vitmains and other molecules plus surrounding medium
- ✓ Formulating optically transparent vitamin solutions
- ✓ Reduction in the quantity of utilized core-shell material
- ✓ Rendering long-shelf life coated vitamins
- ✓ Reinforced physical stability against coalescence and gravitational separations

The capsule size in microencapsulation ranges between 5-300µm in diameter (F. Gibbs, 1999). When the particle size reduces to the nanoscale during nanoencapsulation, surface-to-volume ratio increases. Therefore, the reactions are speeded by many folds; moreover, the mechanical, optical and electrical properties of the materials will also change (Neethirajan & Jayas, 2011). Physicochemical characteristics of vitamins strongly depend on the applied nanoencapsulation approach and delivery system. Thus, an appropriate nanoencapsulation technique must be chosen considering the required size, physicochemical properties, nature of the encapsulated vitamin and the wall material. Nanoencapsulation process is more complex than microencapsulation because of the difficulty in acquiring an intricate morphology for the capsule entrapping the vitamin (Chau, Wu, & Yen, 2007).

According to Gutiérrez, et al., (2013) casein nanoparticles were found to be more stable, cost efficient and environmentally friendly when compared with microemulsions. Moreover, Danino, Livney, Ramon, Portnoy, & Cogan, (2014) and Semo, Kesselman, Danino, & Livney, (2007) suggested that nanoencapsulation via ß-cyclodextrins produced satisfactory sensory properties and created optically transparent solutions, however, microemulsions tend to scatter light. In a recent investigation, it was suggested that nanoliposomes have the benefits to minimize the reactions between bioactives and other molecules, increasing the shelf-life of food products and reducing the amount of used core-shell material compared to conventional liposomes, which are biocompatible and their surface is easily modified (Fathima, Fathima, Abhishek, & Khanum, 2016).

Fig. 1 presents the forms of microcapsuls. The shell is responsible for protecting vitamins from water, oxygen or sunlight. On the other hand, nanostructured delivery forms applied in nanoencapsulation of vitamins are summarized in Fig. 2.

Fig. 1

Fig. 2

There are some commercially approved biopolymers for the encapsulation of vitamins. Starches and cyclodextrins are carbohydrate-based biopolymers that protect these sensitive compounds from the outside environment. Gum Arabic is also used in microencapsulating according to its solubility, viscosity and emulsification features. However, economically it is not profitable. Alginates can also be used as a wall material at environment temperatures. Ethylcellulose has been approved to be a good substance for encapsulating water-soluble vitamins, because as the wall materials width rises, the water permeability of the dispersed vitamins is reduced. Protein based shells may also be utilized in encapsulating different vitamins. Nevertheless, their high cost is limiting factor for using them in an industrial scale.

4. Conventional microencapsulation techniques of vitamins

Before explaining the recent nanoencapsulation techniques applied in protection of vitamins, it is necessary to be familiar with common microencapsulation methods used for different vitamins. Table 1 summarizes the works performed on the microencapsulation of vitamins. In this section, some of the most important techniques plus the literatures are presented.

Table 1

4. 1 Spray-drying

It is one of the oldest encapsulation methods capable of producing encapsulated powders with different particle sizes mostly utilized for encapsulating lipo-soluble vitamins in an industrial scale (Jafari, He, & Bhandari, 2007a). In this procedure, all matrix substances; like, Arabic gum and maltodextrin are drenched and the oil-based material is added during mixing. Later, homogenization is used to achieve an emulsion and finally the yield powder is achieved through spray-drying process. The resulting powder contains 1-50% (w/w) oil (Boyle & Chang, 1999). These microencapsulated vitamins are commonly used in tablets in which oxidation stability and tablet properties are affected by the type of the matrix material. (Shi & Tan, 2002) trapped vitamin D_2 in a chitosan/ethylcellulose coating, and then examined morphology and release traits of the capsuls. *In vitro* results showed that microcapsuls are able to remain unchanged in the intestine juice. High-DE maltodextrins are hygroscopic, thus the produced powder is not desirable. A maltodextrin with a 25DE combined with lactose, galactose or glucose has been shown to extend the shelf life of encapsulated *trans*-ß-carotene compared with commercial 25 DE maltodextrin alone (Desobry, Netto, & Labuza, 1999).

Spray drying has also been applied for encapsulation of water-soluble vitamins too. For example, Ascorbic acid (vitamin C) is an antioxidant or vitamin supplement vastly used in the food and beverage industry, which is so unstable and can be degraded by many mechanisms (Kirby, Whittle, Rigby, Coxon, & Law, 1991). (Desai & Park, 2005) analyzed the encapsulation of vitamin C regarding trypolyphosphate cross-linked chitosan microspheres as the wall material. As a result, cross-linking factor influenced the particle size between 6.1-9µm.

4.2 Spray chilling and spray cooling

Both techniques involve diffusing the vitamins in a molten fat or wax. Next, this dispersion is atomized through heated nozzles into a case at room temperature (spray-cooling) or low temperatures (spray-chilling). At the room temperature, the melting point of the encapsulated material is between 45-122°C. At low temperatures (refrigerate temperature), substances tend to melt at 32-42°C (Risch & Reineccius, 1995). These microcapsuls won't dissolve in water and as the temperature rises, the fat or wax membrane will be molten. Thus, the fat-crystallization in the spray- chilling or cooling process needs to be monitored carefully. This is a suitable technique for encapsulating lipid-soluble vitamins. (Wegmüller, Zimmermann, Bühr, Windhab, & Hurrell, 2006) microencapsulated iron, vitamin A and iodine in hydrogenated palm fat by spray cooling. After 6 months, an excellent stability of retinyl palmitate was observed and losses occurred during this period was nearly 12%.

4.3 Emulsion technique

This process includes dispersing vitamins into an immiscible liquid phase, which possesses the shell material. Second, adjustments are made in order to form shells around the scattered vitamins in the solution. O/W is the most prevalent two phase system applied in encapsulation. (Wang, MacGillivray, & Macartney,

2009) encapsulated cob (III) alamins; like, CNCbl and AdoCbl with 5,6dimethylbenzimidazole and cucurbituril. The cucurbituril combined with vitamin B_{12} imitate the applications of chemical, photochemical and electrochemical of these and other cob (III) alamins. (Leonard, Good, Gugger, & Traber, 2004) encapsulated vitamin E in a breakfast cereal and compared its bioavailability to vitamin E encapsulated in supplements. The capsule was made from d_9-α-tocopheryl acetate (400-IU capsule). Results showed that encapsulated vitamin E in supplements are poorly absorbed; however the bioavailability is increased by using it in fortified-foods. (Van Hasselt, et al., 2009) used polymeric micelles to encapsulate vitamin K. They compared the capsule´s absorption in bile duct legated and sham rats. As a result, the gastrointestinal absorption of the microcapsuls was affected through free bile, furthermore the uptake of micelles via pinocytosis was considered inconsiderable.

4.4 Fluidized bed coating

It is also known as air suspension coating. Solid particles are suspended in an upward moving flow of air which can be either cool or hot. Afterwards, the solid particles are sprayed through the top of the atomized particles of coating wall material, which can be molten or dissolved in an evaporable solvent (Risch & Reineccius, 1995). The coating's material can be cellulose derivatives, dextrins, emulsifiers, lipids, protein derivatives and starch derivatives. This method is prevalent in nutritional supplements that contain encapsulated versions of vitamin C, vitamin B complex and a variety of vitamin/mineral premixes. Moreover, it can be consumed in a variety of food products including: seasonings, fillings, desserts and puddings (Risch & Reineccius, 1995). (Xie, et al., 2010) reported encapsulation of vitamin C using this method with the use of gelatin as the wall material. They fed larval shrimps (*Penaeus japonicas*) with this micro-diet; as a result the wet weight of shrimps rose 300% in 10 to 30 days after hatching. The retention efficiency of vitamin C estimated 88.2% in the coating procedure.

4.5 Liposome entrapment

Liposomes can be defined as single or multi-layered vesicles, which include the complete entrapment of an aqueous phase in a phospholipid-based membrane. Aqueous or lipid-soluble vitamins, but not both are encapsulated in these membranes. (Kirby, et al., 1991) encapsulated vitamin C with high efficiency using this technique. The most stable liposomes are made of lecithin, cholesterol and negatively charged phospholipids. A prevalent method for producing liposomes is dehydration-rehydration and no organic solvents are used.

4.6 Coacervation

In this method, the liquid phase of coating material is separated from a polymeric solution, and the phase is wrapped around the core particles as a uniform layer (F. Gibbs, 1999). It encompasses the dissolving gelling protein and the emulsification of the core compound into the protein. The liquid coating is separated from the polymer solution and is used to cover the material to be encapsulated through controlled physical mixing. It is solidified by thermal, cross-linking or de-solvation methods. Finally, the microcapsuls are obtained by centrifugation or filtration and the results are discrete particles. Coacervation can be simple or complex. The

former, contains merely one colloidal solute like gelatin. The latter, is obtained through the usage of a second oppositely charged hydrophilic colloid such as gelatin and gum acacia or gelatin and polysaccharide (F. Gibbs, 1999). (Junyaprasert, Mitrevej, Sinchaipanid, Boonme, & Wurster, 2001) investigated the effect of process variables on microencapsulating vitamin A palmitate via complex coacervation with gelatin and acacia.

5. Nanoencapsulation technologies applied on different vitamins

According to the recent studies in the field of nanoencapsulation of vitamins, it is expected that in future the novel nanoencapsulation techniques seek to (1) employ naturally occurring food components for encasing bioactives especially vitamins (Chapeau, et al., 2016; David & Livney, 2016; Lee, et al., 2016; Santiago & Castro, 2016), (2) fabricating novel and efficient nanovehicles by the combination of biopolymers, manufacturing nanocomposites, modifying the nanocarriers (Assadpour, Maghsoudlou, Jafari, Ghorbani, & Aalami, 2016; Bochicchio, Barba, Grassi, & Lamberti, 2016; Chapeau, et al., 2016; Lee, et al., 2016; Tan, Feng, Zhang, Xia, & Xia, 2016), (3) exerting novel low energy methods such as, spontaneous emulsification rather than high energy preparation approaches to retain bioactives against harsh processing conditions, decline the surfactant and eliminate the cosurfactant (Assadpour, et al., 2016; Dasgupta, Ranjan, Mundra, Ramalingam, & Kumar, 2016; Mehrnia, Jafari, Makhmal-Zadeh, & Maghsoudlou, 2016) and (4) using novel computational and numerical methods like Monte-Carlo simulations to predict the release profile and optimize targeted delivery of bioactive compounds (Dan, 2016; H. H. Liu, Surawanvijit, Orkoulas, & Cohen, 2016; Malik, Genzer, & Hall, 2015).

In this section, novel methods for nanoencapsulating vitamins are explained. Table 2 and 3 represents different approaches used for nanoencapsulating hydrophilic and lipophilic vitamins, respectively.

Table 2

Table 3

5.1 Nanoemulsification methods

Most prevalent uses of emulsion technology are in aqueous solutions, and nanoemulsions are produced in this medium. Nanoemulsion droplet sizes ranges between 50 to 1000 nm (Sanguansri & Augustin, 2006). There are two ways to prepare nanoemulsions; low energy and high energy techniques such as phase inversion temperature and microfluidization respectively. Nanoemulsions can be used in the liquid state; meanwhile a spray-drying process will be performed to obtain the powder form of the encapsulated material (Jafari, He, & Bhandari, 2007b). Furthermore, it is possible to increase the stability and encapsulation efficiency of the bioactive compounds via multiple emulsions containing a complex of biopolymers (Mohammadi, Jafari, Assadpour, & Esfanjani, 2015).

Different vitamins can be encapsulated and transmitted via nanoemulsions (Gonnet, Lethuaut, & Boury, 2010; Mohammadi, et al., 2015). For instance, (Cho, Seo, Yim, & Lee, 2013) stated that nanoencapsulation of thiamine dilauryl sulfate (TDS), a vitamin B derivative encased with lecithin as an edible encapsulant,

restricted the spore germination of *Fusarium oxypansum* f.sp. Moreover, this compound obstructed its mycelial growth.

There has been some studies in the area of natural surfactants. For instance, (Ozturk, Argin, Ozilgen, & McClements, 2014) encapsulated vitamin D_3 in O/W emulsions with quillaja saponin as a natural surfactant. In the experiment bioacessiblity of vitamin D_3 declined in the following order: corn oil≈ fish oil > orange oil > mineral oil > medium chain triglycerids (MCT). Long chain triglycerids (corn or fish oil) was considered the optimum compound, which enhance the vitamin bioaccessibility.

Double emulsions can be another form of nanoencapsulation of bioactive ingredients (Esfanjani, Jafari, Assadpoor, & Mohammadi, 2015; Mohammadi, et al., 2015). (Bou, Cofrades, & Jiménez-Colmenero, 2014) assessed the physicochemical properties of riboflavin, encapsulated in food-grade $W_1/O/W_2$ double emulsions with different types of lipid sources (chia oil, sunflower oil, olive oil or rendered pork backfat). Riboflavin was effectively encapsulated in chia oil at start, nevertheless the double emulsions in rendered pork backfat protected vitamin B2 more efficiently after 8 days at 4 °C. All in all, double emulsions were stable to the stresses that normally exist in the food industry.

(Hategekimana, Chamba, Shoemaker, Majeed, & Zhong, 2015; Hategekimana, Masamba, Ma, & Zhong, 2015) produced vitamin E- loaded nanocapsuls by octenyl succinic anhydride starches as emulsifiers and wall materials and then stabilized them via spray-drying method. High degree of substitution, low molecular weight and low interfacial tension improved emulsification properties, whereas oxygen permeability and water vapor permeability influenced the film forming characteristics. The degradation profile of vitamin E was best fitted with Weibull model. Overall, low molecular weights formed stable vitamin E nanocapsuls, which can be applied in drug and beverage sector.

(Saberi, Fang, & McClements, 2013) fabricated vitamin E-enriched nanoemulsions via spontaneous emulsification. It can be defined as the formation of little oil droplets when an oil/surfactant mixture is titrated in an aqueous solution. When 30% propylene glycol (PG) or 20% ethanol was present in the aqueous phase, the smallest droplets (d<50nm) and highest transparency were acquired. However, Ostwald ripening occurred as nanoemulsions were unstable during storage especially at high temperatures. Undiluted nanoemulsions showed a high and irreversible increase in turbidity upon heating (53°C) for the system with 30% PG and 38°C for the one containing 20% ethanol. Considering diluted compounds, a much better thermal stability with a high rate in turbidity at 75.5 °C for both systems. The release criteria of poorly water-soluble active vitamin E acetate from oil/water nanoemulsions was reported by (Morais & Burgess, 2014), which used a low energy emulsification method. Nanoemulsions consisted of canola oil, cremophorRH40® and span80®. Dialysis sac and reverse dialysis sac techniques were carried out as well as USP[1] dissolution apparatus fitted with dialysis sac adapters to measure the vitamin E release. Micellar solubilization increased vitamin E transport from canola oil to buffer solution; however no concentration active increase in the

[1] United States Pharmacopeia

nanoemulsion external aqueous phase was seen considering the presence of micelles. (Guttoff, Saberi, & McClements, 2015) prepared vitamin D nanoemulsions through spontaneous emulsification. They investigated the effect of vitamin D and MCT for surfactant to oil ratio, surfactant type (Tween 20,40,60,80 and 85) and stirring criteria on the initial particle size of vitamin D. Results showed that small droplet diameters (d<200nm) was produced using Tween at high stirring speeds (800rpm). These systems were unstable to heating (T>80°C). The thermal stability could be increased by choosing a suitable cosurfactant (sodium dodecyl sulphate).

Assadpour, et al., (2016) nano-encapsulated folic acid (vitamin B_9) in maltodextrin-whey protein double emulsions via spontaneous emulsification method, which is a low energy technique. They utilized Span 80 as a nonionic surfactant in three phase/surfactant proportions (0.2, 0.6 and 1), moreover the applied folic acid amount was 1.0, 2.0 and 3.0 mg/ml in the dispersed phase. In summary, the formulation containing 3mg/ml folic acid in the 12% dispersed phase and water to surfactant proportion of 0.9 was considered as the optimum sample, thus suggesting that spontaneous technique is beneficial in formulating water in oil nanoemulsions.

Dasgupta, et al., (2016) formulated vitamin E acetate nanoemulsions (NE) by edible mustard oil and Tween 80 as surfactant. NE was produced via low-energy wash-out technique, in which there is a continuous addition of the water phase to the oil phase and vitamin E acetate. In conclusion, the nanoemulsions (encapsulation efficiency 99.65%) can be used to improve the shelf life of beverages along with their increased antimicrobial and bioavailability characteristics.

5.2 Nanoliposomes

Hydrophobic/hydrophilic interactions among lipid/lipid and lipid/water interfaces are responsible for the formation of liposomes. Liposomes are formed in single and bilayer arrangements. Lipo-soluble and water-soluble vitamins can be entrapped in these nanocarriers for maintaining their stability in different mediums.

In a study by (Ma, Kuang, Hao, & Gu, 2009), they inserted vitamin E into nanoliposomes with tea polyphenol (water-soluble). The encapsulation efficiencies reported for hydrophobic and hydrophilic agents were 94% and 50%, respectively. The combined nanoencapsulation of vitamin E with vitamin C has also been carried out (Marsanasco, Márquez, Wagner, Alonso, & Chiaramoni, 2011). Liposome's structure was influenced by incubation in buffer solution and stomach pH. The higher absorption of the bioactive compound is attributed to the greater bioavailability of vitamin E.

(Zhou, et al., 2014) produced a drug delivery system using high methoxyl pectin (HMP) or low methoxyl pectin (LMP) coated with vitamin C liposomes. FTIR and morphology assays demonstrated that the hydrogen binding interactions coated pectin to the vitamin C liposomes. Overall, the skin permeation of vitamin C increased 1.7-fold for HMP-L and 2.1-fold for LMP-L after 1 day respectively, whereas vitamin C nanoliposomes showed a lower number. (N. Liu & Park, 2009) used chitosan-coated nanoparticles made

from phosphatidilecholine (pc) and cholesterol (cho) to encase vitamin C. The nanocapsuls contaning pc:cho ratio 60:40 were promising carriers, which had a loading efficiency about 96.5% and a payload of 46.82%.

Tan, et al., (2016) employed composite phospholipid-chitosan to coat the nanoliposomes (chitosomes), which entailed carotenoids, lycopene, ß-carotene, lutein and canthaxanthin. The composite covered the liposomes via layer self-assembly deposition method. To sum up, the biopolymer-covered nanoliposomes protected lutein and ß-carotene to a greater extent compared to canthaxanthin and lycopene. Considering the arrangement of free lipid molecules at the hydrophilic heads and the non-polar membrane core were enhanced, which directly represents the stability of these biopolymer nanoparticles against undesirable conditions; such as, GI stress, etc. Also, Bochicchio, et al., (2016) loaded various vitamins (vitamin E, vitamin B_{12} and vitamin D_2) via nano liposomes including multilamellar large vesicles (MLVs) and small unilamellar vesicles (SUVs). All in all, great encapsulation efficiencies were achieved by both MLVs (between 72% to 95%) and SUVs (between 56% to 76%).

5.3 Nanoprecipitation

This method is also called solvent displacement. In this process, the organic internal phase containing the dissolved vitamin is emulsified into the aqueous external phase. The precipitation of polymer from an organic solution and the diffusion of the organic solvent in the aqueous medium is occurred in this technique (Galindo-Rodriguez, Allemann, Fessi, & Doelker, 2004).

(Khayata, Abdelwahed, Chehna, Charcosset, & Fessi, 2012) produced vitamin E-loaded nanocapsuls via nanoprecipitation technique at laboratory and pilot-scale. The effect of several formulation variables was investigated on the nanocapsuls properties (mean diameter, zeta potential and entrapment efficiency). The optimized formulation of the vitamin E-loaded nanocapsule at laboratory and pilot-scale had the mean diameter of 165 and 172 nm, respectively with a high entrapment rate (98% and 97%, respectively). (Duclairoir, Orecchioni, Depraetere, & Nakache, 2002) encapsulated vitamin E in the matrix of protein fractions of wheat gluten (gliadins). They co-precipitated aqueous ethanolic solution of vitamin E and gliadin in water.

Emulsification-solvent evaporation is an improved sort of solvent evaporation technique which includes emulsification of the polymer solution into an aqueous. Afterwards, the solvent is evaporated and the polymer precipitation remains as the nanoparticles (Reis, Neufeld, Ribeiro, & Veiga, 2006). The size of the particles can be modified by adjusting the stir rate, type and the amount of dispersing substance, viscosity of the phases and temperature. High-speed homogenization and ultrasonication are applied in order to obtain a small particle size (Dehnad, Mirzaei, Emam-Djomeh, Jafari, & Dadashi, 2014).

David & Livney, (2016) engaged potato proteins (Patatin, protease inhibitors and other high molecular weight proteins comprising 40%, 50% and 10% of the whole soluble proteins sequentially) as a natural food-based material to protect and deliver vitamin D_3 (VD) in model beverage solutions. VD was encapsulated within the protein nanoparticles using the liquid antisolvent precipitation method in which two solvents are

employed; one is a good solvent for the bioactive, while the other represents poor solvent activity, finally by adding an antisolvent the bioactive compound is precipitated. To sum up, VD- potato proteins nanocomlexes increased the shelf life of the samples and declined the vitamin loss through pasteurization rendering clear and enriched solutions.

5.4 Solid lipid nanoparticles (SLNs)

It is a nice alternative for nanodispersions. The nanoparticles are produced through congealing. The vitamins are nanoencapsulated in a solid lipid matrix which has a good stability. (Patel, Martin-Gonzalez, & Fernanda, 2012), encapsulated vitamin D_2 (ergocalciferol) using SLNs as the carrier. They observed that the concentration of vitamin D_2 increased, and enhanced dispersion clarity. SLNs also brought protection to vitamin D_2 from oxygen and light. Higher the ergocalciferol loading power, the lower turbidity of the SLN dispersions. (Jenning, Gysler, Schäfer-Korting, & Gohla, 2000) nanoencapsulated vitamin A in SLNs for dermal release. The release kinetic was estimated over a period of 24h via Franz diffusion cells. In the first 6 h, Vitamin A-SLN showed controlled release and in longer periods (12-24h), the release rate exceeded the release rate of comparable nanoemulsions. Drug release is caused due to the decline of amorphous regions in the carrier lattice through a polymorphic transition (ß´→ß).

5.5 Cyclodextrins (CDs)

Liposoluble vitamins can be encapsulated in cage molecules such as CDs or assemblies formed from micelles-like systems. CDs-vitamin combination enhances molecule apparent solubility but the stability depends on pH and dissolution media structure (Lin, Chean, Ng, Chan, & Ho, 2000). Solubility enhancing effect on vitamin A using these capsuls has been reported, like the increase in solubility of all trans retinoic acid in inclusion complexes considering ß-CD and hydroxyl propyl ß-CD (Lin, Chean, Ng, Chan, & Ho, 2000). Vitamin D has also been encapsulated using this technique, by means of ethanol as a common solvent (Soares, Murhadi, Kurpad, Chan She Ping-Delfos, & Piers, 2012).

5.6 Biopolymer nanoparticles

Recently, there have been some studies on nanoencapsulation of food bioactive ingredients including vitamins by nanoparticles made from biopolymers such as milk proteins, gelatin, chitosan, starch and many other natural polymers. For example, (Abbasi, Emam-Djomeh, Mousavi, & Davoodi, 2014) used whey protein isolates (WPI) nanoparticles for encapsulating vitamin D_3 and investigated its stability for 7 days in presence of air. According to their results, nanoparticles had a higher content residual of vitamin D compared to the control sample (water, native WPI and denaturized WPI). Dense structures were produced because of the presence of calcium in the particles, therefore inhibition of oxygen diffusion was also observed in particles. These nanoparticles are applicable in the beverage industry.

In another study, (Penalva, et al., 2015) exerted casein nanoparticles as a surrounding material for folic acid. Lysine and arginine provided the stability of nanoparticles, eventually the mixture was dried through spray-drying. It was observed that the mean size of produced nanoparticles were 150 nm, meanwhile the folic acid

value estimated around 25µg/mg in the nanoparticle. For the *in vitro* release properties, folic acid exposed gastroresistant characteristics and release was possible under controlled intestinal conditions. Regarding *in vivo* studies carried out in this project, laboratory animals were orally administered by this vitamin. Overall, a higher serum could be distinguished in animals treated with casein nanoparticles in which the bioavailability assessed to be 50-52% higher than the traditional solution. At the same time, both bioavailability and release profile of the nanoparticles remained unchanged by high hydrostatic pressure treatment.

Jiménez-Fernández, et al., (2014) produced chitosan-based nanoparticles as a tool to deliver vitamin C to marine organisms. Zebrafish liver cell-line was chosen for *in vitro* studies and *in vivo* studies were done in fish and rotifers to estimate the viable use of nanoencapsulated particles. A significant increase observed in the overall antioxidant capacity of nanoencapsulated-vitamin C in cells, compared to the non-loaded nanoparticles. In post-metamorphic larvae of *S. senegalensis* nanoparticles entered the intestinal epithelium after 2h. In rotifers fed with vitamin C-nanoparticles the level of ascorbic acid raised up to 2-fold in comparison to control groups. (Alishahi, et al., 2011) used chitosan nanoparticles in order to enhance the shelf life and delivery of vitamin C. pH dependency observed in the release of vitamin C, as quick release took place in 0.1 M phosphate buffer solution (PBS, pH 7.4), whereas the release was slow in 0.1 M HCl. As a result, the shelf life of vitamin C was increased by this method and *in vivo* release rate in intestinal tract of rainbow trout was similar to the *in vitro* one.

Lee, et al., (2016) utilized commercial soy protein isolate (SPI) as natural nano-carrier materials, perepared via ultrasonication for 5 minutes, treatment at pH= 12 and using canola oil to protect vitamin D_3 against undesirable conditions, especially when exposed to UV rays. Ultimately, retention of 73.5% was achieved using these natural building blocks compared to the non-coated control (5.2%), which highlights the potential of these nano-vehicles to be used in foods and pharmaceutical industry.

5.7 Coacervation

Coacervation nanoencapsulation technique is based on phase separation because of macromolecules desolvatation. It can get started through environmental changes, which may affect polymer solubility in the solvent, such as; addition of salt or an opposite charged polymer. This process can be adapted to industrial scale (Renard, et al., 2002). (Comunian, Abbaspourrad, Favaro-Trindade, & Weitz, 2014) nanoencapsulated vitamin C via complex coacervation using both gelatin and gum Arabic as encapsulating agents. Low hygroscopicity values were obtained, thus the produced powder could be easily stored and handled. The application and flow of the nanocapsuls were facilitated as they had spherical structures. To summarize, the treatment composed of ratio of 1:1:0.75 of gelatin, gum Arabic and ascorbic acid with 0.025 g/ml of polymer had the best stability at room temperature (20°C).

Chapeau, et al., (2016) used ß-lactoglobulin (BLG) and Lactoferrin (LF) co-assemblies to bind vitamin B_9 (B9). The resulting B9-LF-BLG co-assemblies generated via coacervation and aggregation were thereupon analyzed through compiling screening maps. All in all, B9-LF-BLG coacervates displayed great performance in entrapping vitamin B_9 (≈10 mg B9/g protein), showing that natural food components has a great potential to be utilized as biocarriers in designing functional and healthy foods.

5.8 Electrospinning and Electrospraying

In electrospinning, a polymer solution is provided from a spinneret and produces a droplet at the spinneret exit. Applying an electrical field (10^3 V/cm), the electric charges will gather on the surface of the droplet. Next, the droplets will be deformed by the electric field and they will form a shape of cone, called the Taylor cone. As the field strength increases, a fluid jet originates under the electric field adjacent to the spinneret tip and moves toward the conductive collector (counter electrode). Whipping and circular movements trigger a fast evaporation of the solvent due to the high surface charge jet under the electric field. After the process, solid thin fibers are acquired in the form of nonwoven mats (Kessick, Fenn, & Tepper, 2004). Electrospraying would be defined liquid atomization applied through electrical forces. The difference between these techniques lies in the solution concentration. With this in mind, for low-concentrated solutions the jet attached to cone is destabilized owing to varicose, then the output is fine particles. On the contrary, if the concentration is high the jet is stabilized and the yield will be elongated fibers by whipping instability procedure (Bhushani & Anandharamakrishnan, 2014).

Pérez-Masiá, et al., (2015) successfully applied this technique to nanoencapsulate folic acid, entrapped by whey protein concentrate (WPC) matrix and commercial resistant starch. According to the results, electrospraying yielded smaller particle sizes compared to nanospray-drying. Likewise, WPC capsuls enhanced the bioavailability and stability of folic acid. The answer of this phenomena lies within the interaction between the protein matrix and folic acid which bolsters the stability. Taepaiboon, Rungsardthong, & Supaphol, (2007) encapsulated all-trans vitamin E and retinoic acid via cellulose nanofibers, moreover the encapsulated bioactive compounds showed a gradual release.

Wu, Branford-White, Yu, Chatterton, & Zhu, (2011) encapsulated vitamin C and E, using electrospun polyacrylonitrile nanofibers as the wall material. They demonstrated that this technique has a better sustained release behavior considering bioactive compounds. Vitamin A and E were encapsulated via electrospun cellulose acetate nanofibers having a smooth and round cross-sectional morphology (Taepaiboon, et al., 2007). (Madhaiyan, Sridhar, Sundarrajan, Venugopal, & Ramakrishna, 2013) investigated producing vitamin B12 loaded polycaprolactone nanofiber with constant release of hydrophilic drug as a transdermal delivery procedure. The drug fibers produced through electrospinning technique were observed with SEM for morphology; moreover pore size measurements, mechanical properties and FTIR experiments were also applied on the nano-fibers. The fiber was plasma treated in different periods and made hydrophilic slowly in order to elevate the vitamin release. Due to the drug release profile in PBS buffer *in vitro* medium, the

cyanocobalamin loaded nanofiber considered suitable for transdermal patch. (Sheng, et al., 2013) entrapped vitamin E in silk fibroin (SF) nanofibers. The incorporation of vitamin E improved the protecting ability of SF nanofibrous to protect the skin fibroblast cells against oxidation stress caused by tert-butyl hydroperoxide. These loaded nanofibers, offered an applicative potential for personal skin care, tissue regeneration and the related aspects.

5.9 Ionotropic gelation

This method is based on polyelectrolytes that form cross links in the presence of ions to produce hydrogel beads termed as gelispheres. Gelispheres can be defined as spherical cross linked hydrophilic polymeric entity showing extensive gelation and swelling in simulated bio-fluids. The release of vitamin is controlled by polymer relaxation in this process. As the drug-loaded polymeric solution enters the aqueous solution of polyvalent cations, the hydrogel beads are formed. Next, a 3-dimensional lattice of ionically crosslinked moiety is formed. Bioactive compounds and vitamins are loaded in to these gelispheres so that their natural structures will not be distorted.

Azevedo, Bourbon, Vicente, & Cerqueira, (2014) encapsulated vitamin B_2 using alginate/chitosan nanoparticles. The encapsulation efficiency and loading capacity values of the nanoparticles were 55.9±5.6% and 2.2±0.6%, respectively. Release profiles showed that polymeric relaxation was the most common phenomenon in vitamin B_2 release. Considering the terms of size and PDI (Polydispersity index), vitamin B_2-loaded nanoparticles were more stable than the one's without it. (de Britto, de Moura, Aouada, Mattoso, & Assis, 2012) synthesized nanoparticles containing water-soluble chitosan derivative (N,N,N-trimethyl chitosan, TMC) through ionic gelation with tripolyphosphate (TPP) anions. Three vitamins (B9, B12 and C) were encased by this technique, then zeta potential, morphology and spectroscopy properties were measured. When nanoparticles were loaded with vitamin C, a maximum diameter of 534±20 nm was reached. Moreover, the zeta potential decreased as the vitamins were applied, except vitamin C. They concluded that TMC/TPP nanoparticles are a suitable medium for transporting vitamins in the food sector.

6. Characterization methods for nanoencapsulated vitamins

The most common ways to determine nanoparticles morphology are cryogenic transmission electron microscopy (cryo-TEM), transmission electron microscopy (TEM), scanning electron microscopy (SEM) and atomic force microscopy (AFM). Dynamic light scattering (DLS) is extensively used by scientists to specify the size distribution of vitamin nanoparticles. Zeta potential is measured via laser Doppler anemometry. This factor gives us information about the stability and size of nanoparticles in the *in vitro* environment (Garti, 2008). Considering surface modification of the nanoparticles, Fourier transform infrared spectroscopy (FTIR) is an appropriate method to analyze this feature. High pressure liquid chromatography (HPLC) or spectroscopy at defined wavelengths can be used to determine the quantitative characteristics of entrapped vitamins within nanocapsuls (Garti, 2008).

As an example, Vilanova & Solans, (2015) characterized vitamin A palmitate (VAP) complexed by ß-cyclodextrins (ß-CDs) molecules through FTIR and UV-Vis spectroscopy. According to the spectroscopy results, as the concentration of ß-CDs increased, the solubility of VAP declined continuously, thus a less water-soluble complex will be formed (ultimately two ß-CDs molecules encapsulate a unit VAP molecule). For the investigation of functional groups participating in inclusion complexation, FTIR assay was carried out. As a result, at the bands of 3050 and 950 cm^{-1} (belongs to =CH bond) the double bond was not present showing that the VAP is incorporated within the moiety of =CH section.

7. Controlled release of vitamins through nanoencapsulation

Degradation of polymeric matrix is responsible for releasing the vitamins (passive release) from micro/nanocapsuls, and dispersing the vitamin throughout the matrix (active release). When the vitamin is released, diffusion of the particles plays an important role in this stage. In this period, the vitamins diffuse in the hydrophilic environment (Dan, 2016). Furthermore, water molecules are dispersed through the nanoparticle matrix. Diffusion rate is closely related to the hydrophilicity of the polymeric matrix. Afterward, the vitamin and the nanocapsuls are eroded gradually (Lamprecht, Schäfer, & Lehr, 2001). Initially the vitamins in the nanoparticles are released fast in reaction to the apt environment (burst effect), followed by a more stationary release rate. The burst effect is advantageous when the high releases strengthen the performance of the active particle or it might be hazardous when a constant release rate is expected.

The basic approaches to quantify the release of vitamins are illustrated in Fig 4. The first method (a) uses centrifugation to separate the core material from the nanoparticle suspension; meanwhile the second method (b) uses dialysis or filtration for separation. PBS (phosphate bovine serum) is a common suspension medium, which is applied here. Considering the first method, volume is kept constant by addition of PBS. In the other approach, sample is divided into many sub-samples to study the release profile for the desired period of time. Concentration gradient is kept constant in the second approach for the occurrence of diffusion process.

Fig. 3

The main factors which influence release profile of vitamins are explained below along with the recent investigations.

7.1 Vitamin type and concentration

Chemical and physical interactions such as, hydrophilic-hydrophobic interactions, Van der Waals forces, etc. among the vitamin and polymeric matrix influence the release mechanism of the entrapped agent. The amount of the vitamin is an important factor, which controls the release rate. The higher the amount of the vitamin, the faster the release rate becomes. There are two terms to express the amount of entrapped vitamin. First, the vitamin content is attributed to a mass of vitamins in nanoparticles divided by mass of nanoparticles, expressed in %w/w. An ordinary value for the vitamin quantity ranges between 0.5 to 4% w/w for hydrophilic components, and 10 to 15% w/w for hydrophobic components. Second, the entrapment

efficiency is computed through dividing the content of the vitamin entrapped by theoretical amount of vitamin (the amount first used in nanoparticle formation)(Garti, 2008).

Li, et al., (2012) investigated the effects of whey protein-polysaccharide complexes on the controlled release of vitamin B_2 and vitamin E in double emulsion medium (W/O/W), besides the employed polysaccharides were low methoxyl pectin (LMP) and κ-carageenan (KCG). This study underlines the release rate of lipophilic and hydrophilic vitamins as after the coated capsules were exposed to pancreatin at pH= 7.4; the release rate of both vitamins illustrated somehow similar release rates (≈90%) after 6 h, meanwhile the release profile of vitamin B_2 was a bit higher than vitamin E and lastly the encapsulation efficiency of vitamin E was higher than vitamin B (66% to 64%). Seidenberger, Siepmann, Bley, Maeder, & Siepmann, (2011) controlled the release profile of multiple vitamins (Nicotinamide, riboflavin 5'- phosphate, pyridoxine hydrochloride, thiamine chloride hydrochloride, riboflavin and thiamine nitrate) via the variation of total vitamin concentration. They enhanced the whole vitamin concentration from 10 to 16% and observed that diffusivity was directly proportional to the total vitamin content.

7.2 Biopolymer (variety, copolymer ratio, MW)

Various polymers have been synthesized as nanoparticles. Chitosan, dextran, albumin, pullulan, poly lactic acid (PLA), poly ethyl oxide (PEO), poly caprolactone, poly 3-hydroxybutyrate are typical examples of the natural and synthetic polymers used in nanoencapsulation of vitamins. The break-down of these nanoparticles affect the vitamin release profile. For instance, poly lactic acid, poly lactide-*co*-glycolide acid (PLGA) are nanoparticles which seem to degrade homogenously, while no autocatalysis takes place (Lemarchand, Couvreur, Vauthier, Costantini, & Gref, 2003; Y.-P. Li, et al., 2001; Zweers, Engbers, Grijpma, & Feijen, 2006).

The hydrophilic-hydrophobic ratio of the polymer plays a key role in the release of the entrapped vitamin. For example, PLGA is a hydrophobic complex, consisted of lactide and glycolide monomers. The hydrophilic balance of the PLGA can be changed through altering the copolymer ratio (The most prevalent PLGA molar ratios are: 50:50, 75:25 and 85:15). Thus, the degradation pace will be altered (Bala, Hariharan, & Kumar, 2004). The more hydrophobic the polymer, the stronger interactions between the polymer and bioactive compounds are, so the release process will happen slower. Also, the molecular weight of the polymer affects the release profile, which ranges between a few thousands Da to above 100 000 Da. The higher the molecular weight, the slower the vitamin is released.

To highlight the effect of biopolymer in the release of vitamins, Messaoud, et al., (2016) analyzed the effect of alginate nanocapsules coated with shellac in three different concentrations (1,5 and 10% w/w) and two various coating mechanisms including Ca^{2+} reticulation and acid development on release properties of vitamin B_2. As a result, coated nanocapsules displayed pH-dependant release trend, particularly after binding to calcium cations. By declining pH, the release rate of coated nanovehicles decreased, moreover the 5% w/w

shellac concentration created the best results. However, using the 1% w/w the coating polymer became labile and the 10% w/w caused the alginate membrane to be degraded.

7.3 Nanoparticle size

Nanoparticle size also influences the release process. As the nanoparticles get bigger, their dissociation occurs more slowly. Moreover, the initial burst phase is declined with the slow release according to the slow nanoparticle degradation (Prabha, Zhou, Panyam, & Labhasetwar, 2002). Microparticles are released slower than the nanoparticles according to lower surface toward nanoparticles (Bala, et al., 2004; Panyam & Labhasetwar, 2003).

Kulkarni & Feng, (2013) investigated the effects of nanoparticle size and vitamin E TGPS coating on the release rate and cellular uptake of the nanoparticles across the GI via *in vivo* and *in vitro* assays. They reported that nanoparticle size and the coating substance can considerably alter the nanopartilces release rate and biodistribution. The prepared commercial fluorescent nanoparticles size ranged from 20nm to 500nm, as a result the distribution of nanoparticles were 50nm>200nm>500nm>100nm>25nm, which approves the aforementioned information that as nanoparticles get smaller, the release rate and distribution will become higher. All in all, the 100 and 200nm TGPS-coated nanoparticles efficiently delivered the drugs in the GI cells.

7.4 Environmental circumstances (pH, temperature and release medium)

Environmental conditions alter the release rate and diffusion process. The polymer´s action changes according to the factors like; pH, temperature or other parameters. As an example, poly ortho esters are stable at higher pH (alkaline), while it is disintegrated at acidic pH. Physiological pH is around 7; however, organelles have a distinct pH. Endosomes are more acidic, and lysosomes pH is around 5. Exposing to this pH, the degradation mechanism or polymer configuration initiate, thus the entrapped vitamin will be released. Temperature can also affect the release of the entrapped vitamins. Poly butyl methacrylate and poly *N*-isopropylacrylamide are some examples of temperature release components (Chung et al., 2000).

Recently, Yang, Decker, Xiao, & McClements, (2015) exerted simulated small intestinal fluid (SSIF) medium to examine the release rate and bioaccessibility of vitamin E trapped in O/W emulsions. Applying the medium chain triacylglycerol (MCT) and long chain triacylglycerol (LCT), they noticed that the addition of calcium cations to LCT emulsions will increase the release rate of vitamin E in the prepared medium. Moreover, the degradation rate was higher for MCT-emulsions compared to LCT-emulsions, which highlights the importance of environmental conditions and the encapsulant structure on the release rate.

7.5 Complexation

A decrease in diffusion may result as a response to the polymer and vitamin conjugation, thus the release of the component can hardly take place. As an example, Pereira, et al., (2016) formulated nanoencapsulated vitamin E conjugated with polymeric films including Aloe vera extract, hyaluronic acid, polyethyleneoxide, hyaluronic acid and polyvinyl alcohol to heal skin wounds. To sum up, the polymeric films and their

conjugation effects lead to the prolonged release of vitamin E for the purpose of treating damaged skin tissue.

8. Safety regulations and risks of nanoencapsulated vitamins

Considering food safety, FDA has confirmed the approaches related to the nanotechnology-based food components for mass production (Chau, et al., 2007). However, questions are being posed that the increased bioavailability, uptake and modified biokinetics of the nanosized vitamins might be hazardous to the biological system. It is assumed that biodegradable natural materials which are used for nanoencapsulation are considered low-risk compared to synthesized polymeric nanocapsuls. Until now, ambiguities on consuming nano-scale food materials still exist, besides their effects on human health and environment needs to be further analyzed (Dowling, 2004).

Still, there is no certain legislation in which nanomaterials (especially encased vitamins) in food industry are markedly addressed; nevertheless agencies and government insist that current legislations made by them ensure the safety of nano-food products (Amenta, et al., 2015).

8.1 An overview of nano regulations in different countries

In 2011, a guidance document entitled “Guidance for the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain” was prepared by The European Food Safety Authority (ESFA). In essence, this guidance provides as assessment for the risks of employing nanomaterials in food products. Nevertheless, considering the physico-chemical properties of the nanomaterials, these minute particles are also needed to be analyzed in five stages: (a) When prepared; (b) for the usage in food product; (c) within the food network; (d) In the toxicity assays; (e) inside the biological fluids and cells.

Another important factor, which should be considered, is the interactions occurred between nanomaterials and food structure. Regarding the catalytic function of the nanomaterials, radical oxygens or photoreactions might be formed, thus these factors should be carefully characterized within the nanofood products.

According to the EU principle suggested in December 2011 (Amenta, et al., 2015), engineered nanomaterials (ENM) should be mentioned in the label of nano-food products. This legislation was considered to be exerted till in December 2014. Regarding article 2 from this legislation, ENMs are considered to be 100nm or less in one or more dimensions either inside or at the surface moreover aggregates or agglomerates above the size of 100nm, which represent the nano characteristics, are also referred as ENMs.

The US Food and Drug Administration (FDA) believes that emerging nano-food products can be regulated under its authorities, nevertheless there is not a delicate principle attributed to the nanomaterials within food industry. On the other hand, this organization has prepared a guidance for the manufacturers entitled “Draft Guidance for Industry” regarding the safety and regulatory issues in novel food industry technologies (FDA, 2011). This definition of nanomaterials described by this draft guidance is mentioned below:

- Agents or products lying within the nanoscale range at least in one dimension (from 1 to 100nm).

- Agents or products that reveal physical, chemical and biological characteristics related to the nanomaterials, albeit they are not nano-sized.

Besides, the guidance has defined some responsibilities for the manufacturers, which are as follows:

- Monitor the changes being exerted to the food materials; such as, physicochemical properties and impurities.
- Evaluate the safety of food products after their modifications.
- Submit a regulatory assessment to US FDA
- Specify a regulatory issue for the consumption of the novel food product

Regarding the mentioned guidance, USA FDA insists that the current legislations are adequate for evaluating nanomaterials safety, moreover the organization accentuates that all manufactured nano-food products should be approved in accordance with the principles present in their guidance.

The regulatory organization of other countries including Australia and New Zealand (FSANZ), and Korea (MFDS) believe that food products treated with nanomaterials should be evaluated through safety experiments before releasing in the food market and they have published some related guidelines too.

8.2 Nanoparticles fate in the digestive system

In general, after the oral administration of the nanoparticles, three options are considered for both the vitamin and the nanocapsule/matrix (Fig 4):

1. The nanoparticle plus the vitamin are released in the gastrointestinal (GI) tract and full digestion with absorbance is carried out. At the same time, the surfactants used in the complex should be assessed through safety assays.

2. Nanovehicles will be broken down partially; therefore the encapsulated vitamin is released slightly. Moreover, conjugates will be formed between the residual nanovehicles and the vitamin, hence different traits and biokinetic behavior is expected from these conjugates. Another possible risk is that these unknown conjugates may translocate to the other organs because of their miniature size. It is possible that these compounds may act as allergens and trigger immunogenic responses in human body. With this intention, further studies need to be performed for evaluating the absorption, distribution, metabolism and excretion (ADME) data regarding the nonovehicle-vitamin complexes. For example, gelatin nanoparticles are formed via cross-linking which cause immunogenic responses and the content of antibodies will rise in this situation. As stated before, immunological concerns are more likely to happen in a multicomponent formulation rather than a uniform structure.

3. The nonovehicle is resistant to digestion, and then vitamins are not released in the GI tract. Here two options are assumed:

a. The nanoparticle plus the core material is thoroughly excreted from the GI tract. However, this is not a suitable option; hence the engineered nanomaterial would not be commercially useful in the food sector (Sabliov, 2015).

b. Due to nanosize scale, the nanovehicle and entrapped vitamin can pass the biological barriers in the intestine and enter the circulatory system. This is where immunologic and toxicokinetics assays may be crucial. When a nanoengineered carrier is applied in the food sector, investigations must be done to evaluate its biodistrubution properties, toxicological effects and improper alterations in the nanoengineered material properties (Sabliov, 2015).

To sum up, a precise design for nanovehicles can mask the safety problems to a great extent and the safety can be assessed in a straightforward approach. Moreover, being conscious in full features of safety concerns are the key to a better design and to make commercially nanodelivery systems possible.

Fig. 4

9. Conclusions and future trends

Nanoencapsulation of vitamins with different techniques is expected to be a crucial field of research in the following years. By entrapping several vitamins in the nanocapsuls, a synergistic effect can be achieved that enriches human food. Techniques like nanoemulsification, coacervation, nanoprecipitation, nanoliposomes and solvent evaporation are enduring methods for nanoencapsulating not only vitamins but also other ingredients. Furthermore, solvent evaporation and nanoprecipitation remains to be exclusive approaches to encapsulate lipophilic vitamins. Nonetheless, all these techniques require suitable drying methods in order to produce nanoencapsulates in the powder form. Today, spray-drying and freeze drying are widely used as drying methods in order to nanoencapsulate the bioactive materials, especially vitamins. The disadvantages of freeze drying and spray-drying are the high costs and changes needed for retaining the nanoparticle size, respectively. Therefore, special apparatuses are required to produce the nano-sized powders. Besides, each encapsulation technique has its own operating characteristics that influence the final nano product. Most of the nanoencapsulated products have represented excellent bioavailability. The release of the vitamins is considerably related to the nanoparticle size among the other physical features, thus many scientists are trying to decline the size of the nanoparticles due to the increase in the surface and better absorption in the epithelial cells. More work need to be done on carefully designing the nanoparticle to interact in the appropriate conditions (i.e. pH, temperature). Challenging questions might come up with this end; like synthesizing novel nanopolymers for optimizing the delivery process. Furthermore, the safety of vitamin nanoencapsulation in food needs further investigation. It includes the complicated interactions among nanoparticles and the cellular system. Finally, the process of the delivery in the reaction site needs to be carefully studied.

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Table 1. Microencapsulation techniques for different vitamins

Microencapsulation technique	Wall material	Vitamin	Purpose	Reference
Spray-drying	Granules of rice starch & gum Arabic	Vitamin C	Examining the stability of ascorbic acid and determining the size distribution of microcapsuls	Trindade & Grosso, 2000
Spray-drying	Trypolyphosphate cross-linked chitosan microspheres	Vitamin C	Investigating the release rate and stability in the capsule	Desai & Park, 2005
Liposome	Egg phosphatidylcholine, cholesterol, DL-α-tocopherol	Vitamin C	Comparing the half-life of pure vitamin C and capsulated one	Kirby *et al.*, 1991
Emulsion technique	Starch, Glycerin of vegetable origin, Carrageenan, Disodium Phosphate, Medium Chain Triglycerides	Vitamin E	bioavailability of vitamin E in fortified breakfast cereal	Leonard *et al.*, 2002
Spray-drying	Chitosan/ethylcellulose	Vitamin D_2	Morphology and release properties of the microcapsuls	Shi & Tan, 2002
Emulsion technique	$mPEG_{5000}$-b-p(HPMAm-lac_2), a thermosensitive block copolymer	Vitamin K	Evaluating the influence of bile acids on the oral bioavailability	Van Hasselt *et al.*, 2008
Emulsion technique	A-axial 5,6-dimethylbenzimidazole ligand with cucurbit-7-uril	Vitamin B_{12}	Stabilizing cob(III)almins such as CNCbl and AdoCbl with the suggested capsuls	Wang *et al.*, 2009
Fluidized bed coating	Gelatin	Vitamin C	Encapsulation efficiency and microdiet effect on larval shrimps	Xie *et al.*, 2010
Coacervation	Gelatin and gum Arabic	Vitamin A	Effect of process variables on the encapsulation process	Junyaprasert *et al.*, (2001)
Spray-drying	Starch and ß-cyclodextrin	Vitamin C	Analyzing the encapsulation efficiency and the degradation of ascorbic acid	Uddin *et al.*, (2001)
Spray cooling	Fully hydrogenated palm fat and 1% lecithin	Vitamin A	Food fortification to combat health problems in developing countries	Wegmüller *et al.*, (2006)

Table 2. Examples of nanoencapsulated hydrophilic vitamins

Nanoencapsulation technique	Wall material	Hydrophilic vitamin type	Purpose	Reference
Coacervation	lactoferrin and ß-lactoglobulin co-assembly	Folic acid (vitamin B_9)	Designing a naturally occurring biocarrier for vitamin B_9	Chapeau *et al.*, (2016)
Nano emulsification (Spontaneous)	maltodextrin-whey protein double emulsions	Folic acid (vitamin B_9)	Exerting a low-energy method to encapsulate Folic acid (vitamin B_9)	Assadpour *et al.*, (2016)
Nano-liposome	L-α-Phosphatidylcholine, Cholesterol and egg yolk lecithin	Vitamin B_{12}	Fabricating multi/uni lamellar food-grade nanoliposomes to encase three different vitamins	Bochicchiu *et al.*, (2016)
Ionotropic gelation	Alginate/chitosan nanoparticles	Vitamin B_2	Evaluating encapsulation and controlled release of vitamin B_2 considering the wall materials	Azevedo *et al.*, (2014)
Electrospraying and Nanospray drying	Whey protein concentrate (WPC) and commercial resistant starch	Folic acid (Vitamin B_9)	Analyzing the encapsulation yield and stability	Pérez-Masiá *et al.*, (2014)
Coacervation	Casein nanoparticles	Folic acid (Vitamin B_9)	Evaluating the oral bioavailability through *in vitro* and *in vivo* studies	Penalva *et al.*, (2015)
Ionotropic gelation	Chitosan-based nanoparticles	Vitamin C	Investigating the loaded and non-loaded vitamin C nanoparticles in marine organisms	Jiménez-Fernández *et al.*, (2014)
Ionotropic gelation	Chitosan nanoparticles	Vitamin C	Extending shelf life and delivery of vitamin C	Alishahi *et al.*, (2010)
Ionotropic gelation	Water-soluble chitosan derivative (N,N,N-trimethyl chitosan, TMC)	Vitamins B_9, B_{12} and C	Incorporating stabilized vitamins into biopolymeric nanoparticles especially for food applications	Britto *et al.*, (2011)
Electrospinning	Electrospun polyacrylonitrile nanofibers	Vitamin C	Fabricating core-shell nanofibers encapsulating vitamins for photoprotection	Wu *et al.*, (2011)
Electrospinning	Polycaprolactone nanofiber	Vitamin B_{12}	Investigating water-soluble vitamin delivery with hydrophobic polymer nanofibers for transdermal applications	Madhaiyan *et al.*, (2013)
Coacervation	Gelatin and gum Arabic	Vitamin C	Studying transparent solid matrices resulting from the dehydration of new protein gels	Renard *et al.*, (2002)
Cyclodextrins	Dextran nanoparticles	Vitamin B_{12}	Optimizing the effectiveness of vitamin B_{12} conjugates with various levels of cross linking	Kishore *et al.*, (2007)
Nano-liposome	Soy phosphatidylcholine	Vitamin C	Investigating liposomes as vitamin transporters incorporated in orange juice	Marsanasco *et al.*, 2011
Nano-liposome	High methoxyl pectin (HMP) and low methoxyl pectin (LMP)	Vitamin C	Studying transdermal drug delivery to acquire a better storage ability and skin permeation	Zhou *et al.*, (2013)

Nano-liposome	Chitosan nanoparticles	Vitamin C	Improving the vitamin hydrophobicity and stability in the delivery system	Liu and Park (2009)
Nano emulsification	Lecithin	Thiamine dilauryl sulfate (TDS), a vitamin B derivative	Inhibiting spore germination of *Fusarium oxysporum* f. sp. *Raphani* using TDS in nanocapsuls	Cho *et al.*, (2013)
Nano emulsification	$W_1/O/W_2$ double emulsions with 4 different lipid sources	Vitamin B_2	Using this process as functional healthier-fat food ingredients	Bou *et al.*, (2014)

Table 3. Examples of nanoencapsulated lipophilic vitamins

Nanoencapsulation technique	Wall material	Lipophilic Vitamin type	Purpose	Reference
Nanoprecipitation	Potato proteins	Vitamin D_3	Utilizing potato proteins as natural nanovehicles for the encapsulation of vitamin D_3	David and Livney (2016)
Nano emulsification	Edible mustard oil with Tween-80	Vitamin E	Employing a simple and low energy method to formulate nanoemulsions with vitamin E	Dasgupta *et al.*, (2016)
Nano-liposome coated by chitosan (chitosome)	Egg yolk phospholipid with Tween 80 and chitosan	ß-carotene	Developing a novel structure for an efficient delivery of ß-carotene	Tan *et al.*, (2016)
Nano emulsification	Soy protein isolate plus canola oil	Vitamin D_3	Treatment of soy protein isolate to prepare resistant nano structures	Lee *et al.*, (2016)
Nano-liposome	L-α-Phosphatidylcholine, Cholesterol and egg yolk lecithin	Vitamin E and D_2	Fabricating multi/uni lamellar food-grade nanoliposomes to encase three different vitamins	Bochicchiu *et al.*, (2016)
Electrospinning	Cellulose nanofibers	Vitamin A and E	Using nanofibers as carriers for delivery model of vitamins	Taepaiboon *et al.*, (2007)
Electrospinning	Electrospun polyacrylonitrile nanofibers	Vitamin E	Fabricating core-shell nanofibers encapsulating vitamins for photoprotection	Wu *et al.*, (2011)
Electrospinning	Silk fibroin (SF) nanofibrous mats	Vitamin E	Fabrication and viewing the skin benefit of vitamin E loaded with these nanofibers	Sheng *et al.*, (2013)
Cyclodextrins	ß-CD and hydroxyl propyl ß-CD	Vitamin A	To produce All-trans-retinoic acid with high aqueous solubility	Lin *et al.*, 2000; Qi and Shieh, 2002
Cyclodextrins	Dextran nanoparticles	Vitamin D	Encapsulating vitamin D to increase its regulation of body weight effect	Soares *et al.*, 2012
Solid lipid nanoparticles (SLNs)	Tripalmitin	vitamin D_2 (ergocalciferol)	Increasing the stability of vitamin D_2 to enrich milk and margarine	Mandar and Martin-Gonzalez (2012)
Solid lipid nanoparticles (SLNs)	Glyceryl behenate	Vitamin A	Sustained release for the skin over a prolonged period of time	Jenning *et al.*, (2000)
Nanoprecipitation	Polycaprolactone and vitamin E dissolved in acetone	Vitamin E	Preparing vitamin E nanocapsuls at lab-scale and pilot-scale	Khayata *et al.*, (2011)
Nanoprecipitation	Matrix of protein fractions of wheat gluten (gliadins)	Vitamin E	Protecting vitamin E against light, heat and oxygen	Duclairoir *et al.*, (2002)
Nano-liposome	Soy phosphatidylcholine	Vitamin E	Investigating liposomes as vitamin transporters in orange juice	Marsanasco *et al.*, 2011
Nano emulsification	Octenyl succinic anhydride (OSA) modified starches	Vitamin E	Investigating physicochemical stability and thermal degradation of vitamin E	Hategekimana *et al.*, (2015)
Nano emulsification	O/W emulsions containing saponin as a surfactant	Vitamin E	incorporating vitamin E into functional foods and beverage products	Yang and McClements (2012)
Nano- emulsification	Medium chain triglyceride oil (MCT)	Vitamin D	Investigating particle size and stability of vitamin D	Guttoff *et al.*, (2014)
Nano emulsification	Whey protein isolate	Vitamin D_3	Studying the stability of vitamin	*Abbasi et al.*,

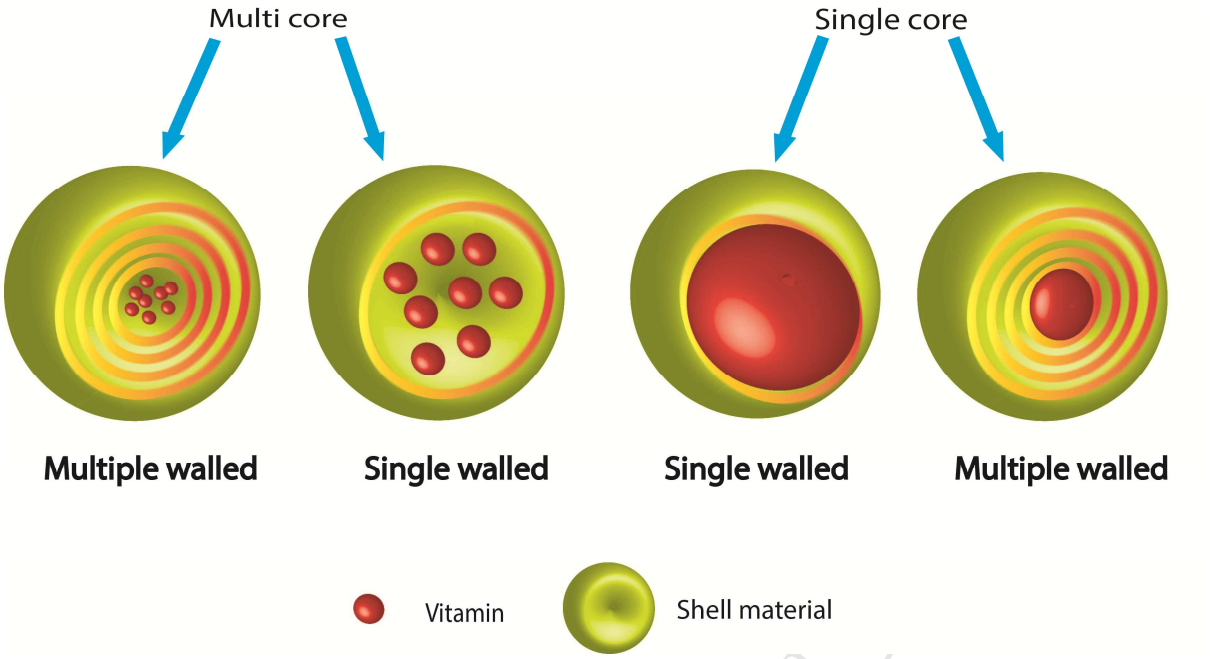
	(WPI) nanoparticles		D_3	(2013)
Nano emulsification	Canola oil and Span80®	Vitamin E acetate	Developing a practical HPLC method to estimate vitamin E	Morais *et al.*, (2014)
Nano emulsification	Medium chain triglyceride oil (MCT)	Vitamin E	Studying the influence of cosolvents on formation and stability of vitamin E	Saberi *et al.*, (2013)
Nano emulsification	Carrier oil (MCT, corn oil, fish oil, mineral oil or orange oil)	Vitamin D_3	Emulsifying and stabilizing capacities of natural surfactants	Ozturk *et al.*, (2014)

Fig. 1. Microcapsule forms applied in vitamin encapsulation.

Fig. 2. Types of nanostructured delivery systems applied in vitamin encapsulation.

Fig. 3. Prevalent approaches used to determine *in vitro* vitamin release profile

Fig. 4. Remarking the safety evaluation for vitamin Nanocarriers. GIT, gastrointestinal tract; ADME, adsorption, distribution, metabolism and excretion



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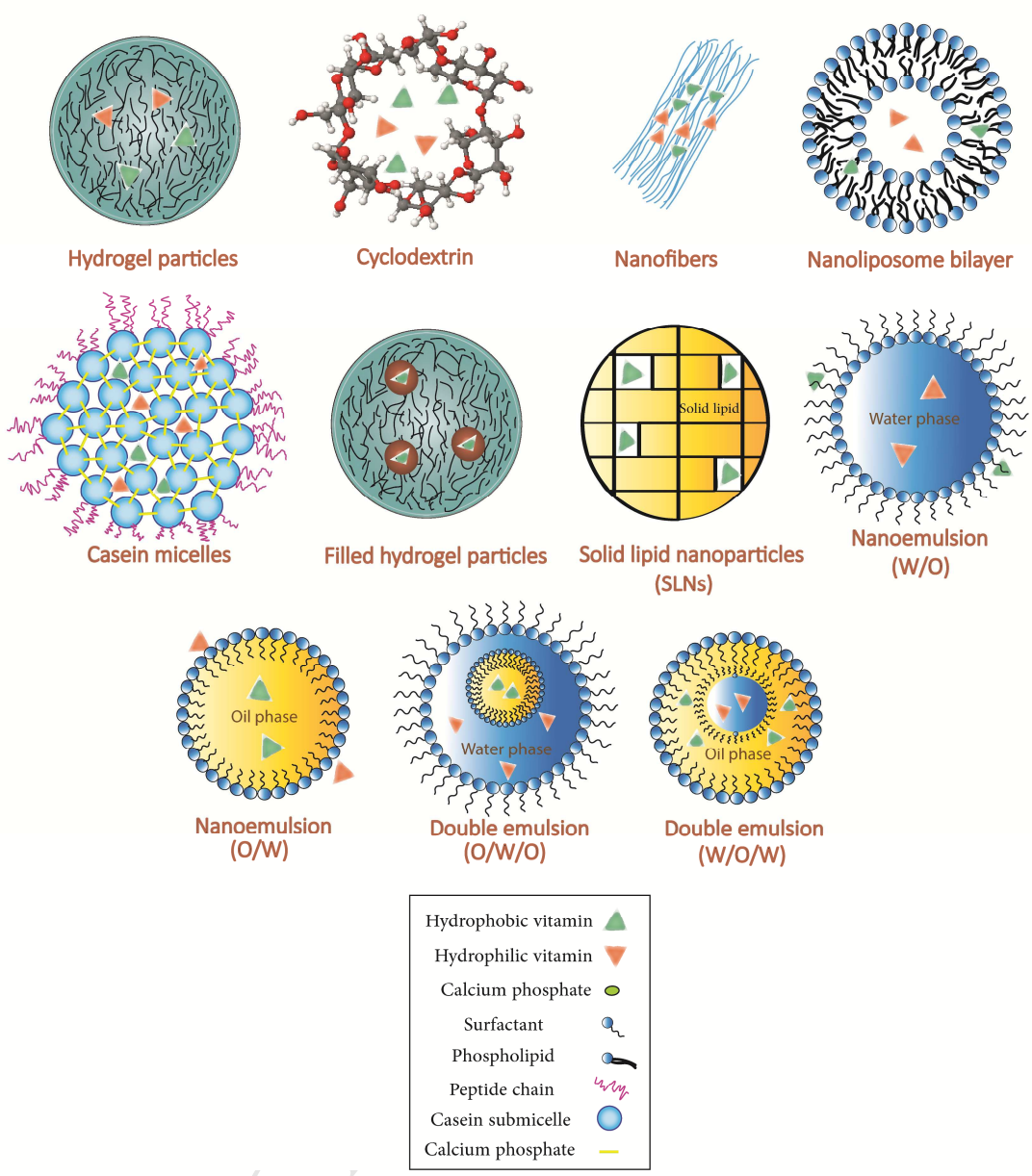

Fig. 2. Types of nanostructured delivery systems applied in vitamin encapsulation.

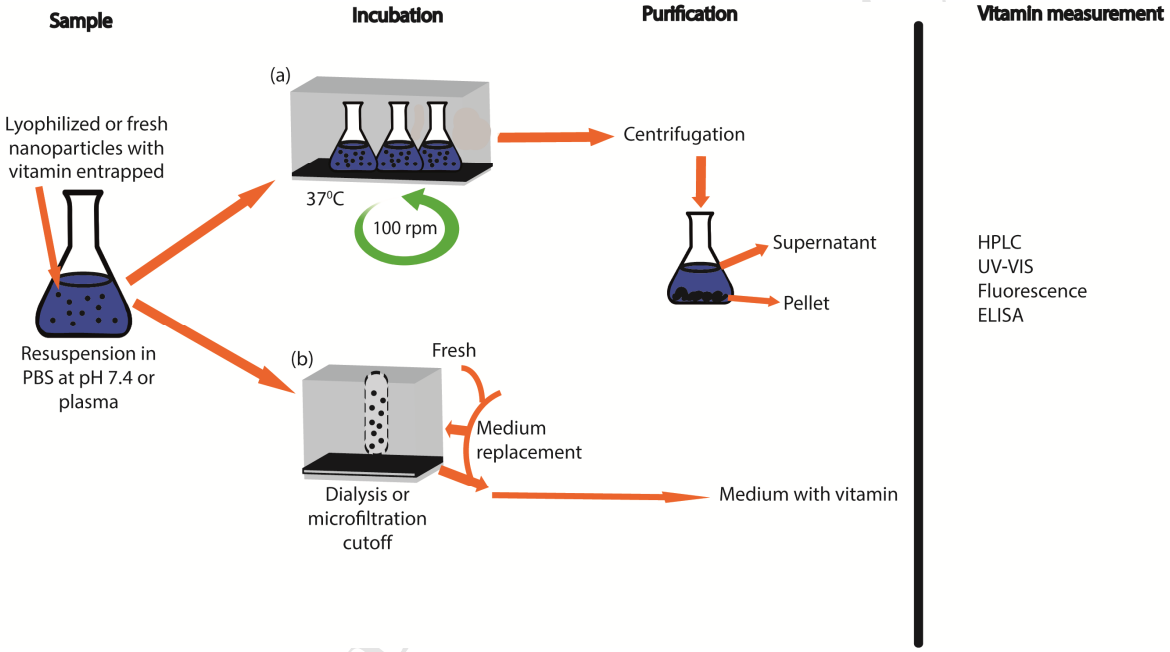

Figure 3. Prevalent approaches used to determine *in vitro* vitamin release profile

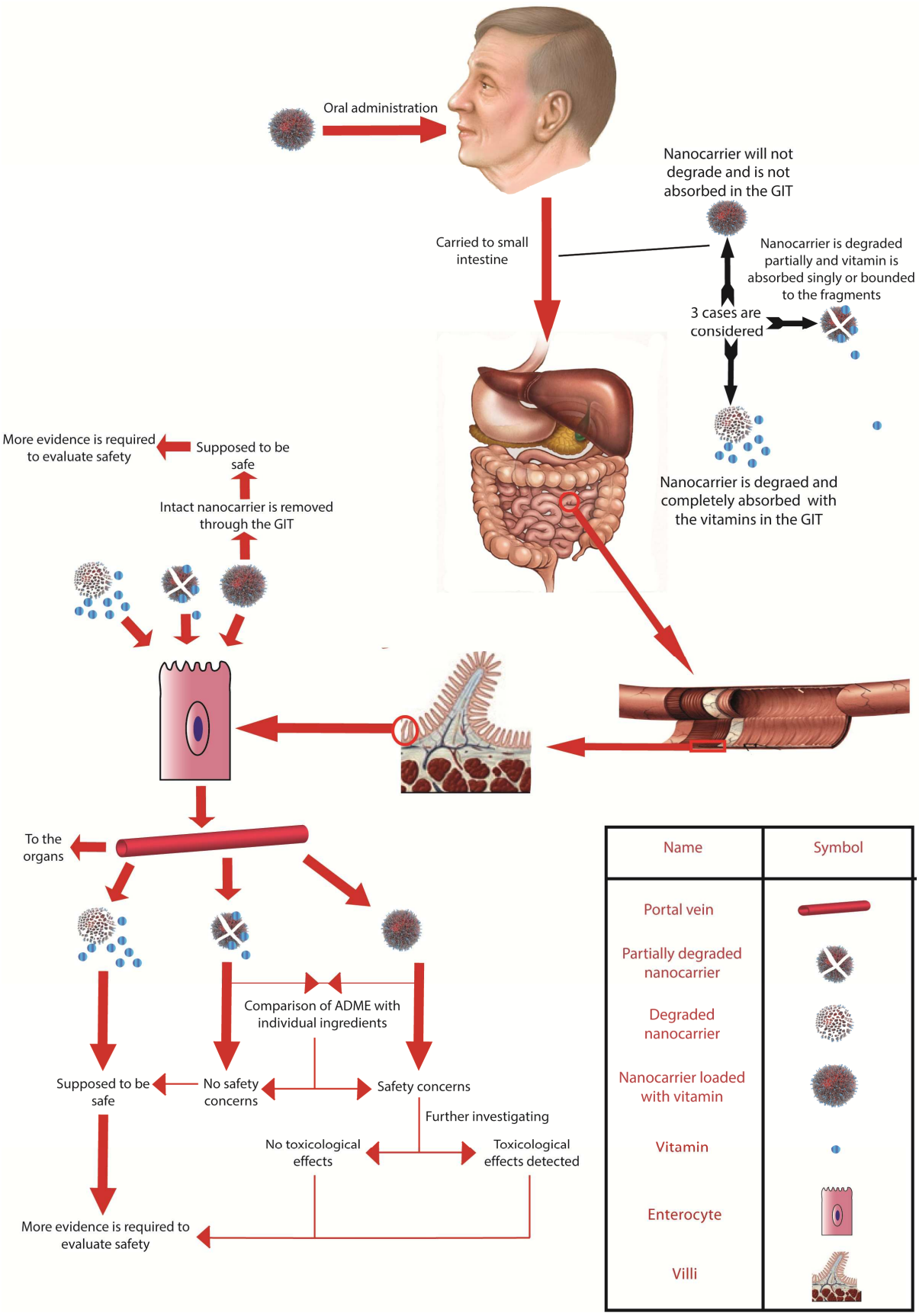

Figure 4. Remarking the safety evaluation for vitamin Nanocarriers. GIT, gastrointestinal tract; ADME, adsorption, distribution, metabolism and excretion

Research Highlights

- Importance of vitamin nanoencapsulation is compared to microencapsulation.
- Microencapsulation techniques applied in vitamins are discussed.
- Nanoencapsulation methods and nanocarriers applied in vitamins are reviewed.
- Factors influencing the release rate of vitamins are highlighted.
- Safety and risk evaluation issues are analyzed.