β-Carotene within Loaded Delivery Systems in Food

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Nanotechnology has opened new opportunities for delivering bioactive agents. Their physiochemical characteristics, i.e., small size, high surface area, unique composition, biocompatibility and biodegradability, make these nanomaterials an attractive tool for β-carotene delivery. Delivering β-carotene through nanoparticles does not only improve its bioavailability/bioaccumulation in target tissues, but also lessens its sensitivity against environmental factors during processing. Regardless of these benefits, nanocarriers have some limitations, such as variations in sensory quality, modification of the food matrix, increasing costs, as well as limited consumer acceptance and regulatory challenges.

Keywords: beta-carotene ; bioavailability ; delivery system ; encapsulation ; engineered nanomaterial ; SLNs ; NLCs

1. Introduction

Vitamin A deficiency is one of the most diagnosed micronutrient deficiency disorders worldwide, especially in developing countries. However, its magnitude is more widespread in the vegetarian population [1]. Across the globe, approximately 250 million preschool children are estimated to be affected by vitamin A deficiency [2]. Furthermore, occurrence of disease has an intimate relationship with a low antioxidant load in the daily diet. Furthermore, lifestyle (exercise, smoking, drinking and high consumption of meat-based and processed foods), environment (emotional and social stress), and cultural constraints trigger the expression of housekeeping genes to adopting genes to retain the cellular, organ or body homeostasis [3]. The aforesaid stimuli also cause the generation of reactive oxygen species (ROS), resulting in oxidative homoeostasis imbalance at cellular and tissue levels, thus generating oxidative stress [4]. Oxidative stress can be defined as a phenomenon triggered by an imbalance between the generation and accumulation of ROS. In general, ROS, including organic hydro peroxides, hydrogen peroxide, nitric oxide, hydroxyl radicals and superoxide, are generated as by-products of oxygen metabolism; in addition, these environmental stimuli (UV, pollutants, heavy metals, and xenobiotics (including antiblastic drugs, antiallergic drugs, immunosuppressant drugs) equally contribute to ROS production, thus causing oxidative stress [5]. Accruing scientific evidence is accumulating on the involvement of oxidative stress in the occurrence of several health complications, which are attributed to inactivation of metabolic enzymes and damage vital cellular components, oxidization the nucleic acids, resulting in eye disorders, atherosclerosis, cardiovascular diseases, joint and bone disorders, neurological diseases (amyotrophic lateral sclerosis, Parkinson's disease and Alzheimer's disease) and misfunctioning of different organ including lung, kidney, liver and reproductive system [6]. ROS are primarily generated in mitochondria under both pathological as well as physiological conditions [7]. Cells activate an antioxidant defensive system which primarily includes enzymatic components such as superoxide dismutase, glutathione peroxidase, and catalase in order to minimize the oxidative stress cell [8].

1.1. Oxidative Stress and Antioxidants

ROS generation is attributed to both nonenzymatic and enzymatic reactions. Enzymatic processes that have intricate involvement in the respiratory chain, phagocytosis, prostaglandins biosynthesis, and cytochrome P450 system are responsible for ROS generation. Superoxide radicals produced as the result of enzymatic action of NADPH oxidase, peroxidases and xanthine oxidase initiate the chain reaction for ROS formation including hydrogen peroxide, hydroxyl radicals, peroxynitrite, hypochlorous acid and so on [9]. Hydroxyl radicals ($^{\bullet}OH$) are considered as the most reactive among all ROS in vivo and are produced as a result of catalysis of H_2O_2 in the presence of Fe^{2+} or Cu^{+} (Fenton reactions).

In addition, some nonenzymatic processes also contribute to ROS generation, especially when oxygen is either exposed to ionizing radiations or reacts with organic compounds. ROS are produced due to exogenous and endogenous sources. Exogenous sources of ROS include inflammation, immune cell activation, infection, ischemia, cancer, mental stress, excessive exercise and aging [4][10]. Exogeneous ROS generation relies on exposure to radiation, heavy metals [11], environmental pollutants [12], certain drugs (bleomycin, cyclosporine, gentamycin, tacrolimus) [13], toxic chemical and solvents [13], food processing (used oil and fat and smoked meat) [14], cigarette smoking and alcohol consumption, among

other [10]. ROS are essential part of several biological processes when they remain at low or moderate concentrations. For instance, these ROS are obligatory for synthesis of some cellular structures, which have vital role in the host defense system, i.e. in the defence of pathogens [14][15]. In fact, macrophages synthesize and store ROS to kill pathogenic microbes [16]. The critical role of ROS in the immune system is well recognized as patients unable to produce ROS are more prone to pathological infections [17]. In addition, ROS are also integrated in an array of cellular signaling pathways as they play a regulatory role in intracellular signaling cascades, including endothelial cells, fibroblasts, cardiac myocytes, vascular smooth muscle cells and thyroid tissue. Nitric oxide (NO) is considered as a key cell-to-cell messenger, which plays a vital role in cell signaling and is intricately involved in several processes, such as blood flow modulation, thrombosis and normal neural functioning [18]. Nitric oxide also demonstrates close association with nonspecific host defense in eliminating the tumor cells, as well as intracellular pathogens [19]. In addition to beneficial effects, ROS also pose several negative impacts by affecting cellular structure, including plasma membrane, proteins, lipoprotein, proteins and nucleic acids (deoxyribonucleic acid, DNA; ribonucleic acid, RNA). Oxidative stress is a result of ROS imbalance between its rate of generation and rate of clearance within the cell [20]. These excess ROS thus cause damage in the plasma membrane by lipid peroxidation and form malondialdehyde and conjugated dienes which are cytotoxic and mutagenic in nature. Being a chain reaction cascade, lipid peroxidation spreads very rapidly, damaging a significant number of lipids, proteins and nucleic acids, hence hampering their functionalities [21]. In summary, ROS impart beneficial effects when they are maintained at low or moderate concentrations while they negatively affect several cellular structures at higher concentrations.

The human body adopts several strategies to combat the negative effects generated due to oxidative stress, including enzymatic (superoxide dismutase, glutathione peroxidase and catalase) or nonenzymatic (L-arginine, glutathione, coenzyme Q10 and lipoic acid) antioxidant molecules. In addition to the aforesaid molecules, several exogenous antioxidants molecules from animal or plant origins are deliberately incorporated, i.e. fortified, into the diet [5].

1.2. Mode of Action of β-Carotene against Oxidative Stress

β-Carotene, a key member of the carotenoid family, is recognized as one of the most potent antioxidants [22] and the major provitamin A carotenoid available in the human diet. The health benefits of β-carotene are attributed to its given biological properties [21]: (a) as antioxidants that scavenge and quench ROS of oxidative metabolism, (b) as provitamin A compounds that activate retinol-mediated pathways, (c) as electrophiles that boost endogenous antioxidant systems, (d) by hampering inflammation-related processes mediated by nuclear factor κ-light-chain-enhancer of activated B cell (NF-κB) pathway, and/or (e) by directly binding nuclear receptors (NRs) and other transcription factors in target cells.

Retinoic acid acts as ligand for the retinoid X receptors (RXRs) and canonical retinoid acid receptors (RARs), which influence the expression of a number of responsive genes and have intimate relationships with fatty acid, cholesterol, Ca^{2+} and phosphate homeostasis [23]. β-Carotene also demonstrated tumor cell suppression activity and enhanced intercellular communication at gap junctions [3]. It is believed that consumption of β-carotene may cause low incidence of hepatic oxidative stress and lipid oxidation. The assumption was supported by a mice model study where expression of 1207 genes (approximately 4% genes) of a total of 30,855 genes in a hepatic transcriptome was influenced when mice were fed with β-carotene as compared to control mice [24]. Remarkably, numerous differentially expressed genes were intimately involved in energy metabolism, lipid metabolism, and mitochondrial redox homeostasis.

β-Carotene is the main contributor to vitamin A in human beings, if preformed vitamin A intake is insufficient. It acts as a precursor of vitamin A, with the potential to yield two retinal molecules following cleavage by beta-carotene oxygenase 1 in the intestine, as compared to other carotenoids which generally yield only one retinal molecule. Despite its indispensable role in vision, it may furthermore play a role as a bioactive compound, due to its potential antioxidant effects [25], and its interaction with nuclear receptors, mainly RAR/RXR, which is important for cell differentiation and immunity [26]. These properties make β-carotene one of the most investigated biological molecules, both in academia and industry. Though its multifunctionality in humans is yet to be fully understood, several epidemiologic studies have demonstrated its relationship to a decreased incidence of chronic diseases such as blindness [27], xerophthalmia [28], cancer [29], cardiovascular diseases [30], diabetes [31] and premature death [32] and found to have an antioxidant component.

2. Delivery Systems for β-Carotene

β-Carotene is often used as a natural colorant and additive in food in spite of having poor water solubility, a high melting point, susceptibility to environmental conditions, chemical instability, heterogenous distribution in food matrices, and low bioavailability—all factors that limit its potential for the food industry. In this regard, encapsulation techniques have allowed

researchers to develop a range of delivery systems with desired functionalities, such as enhanced stability, high dispersibility, improved solubility and targeted/controlled release and improved bioavailability [33][34].

Delivery system is the technology where a bioactive ingredient is enclosed in nano-/microstructure not only to protect bioactive compounds against environmental degradation (oxidation, pH and enzyme), but also to release them at a particular target site in a defined rate [35]. At present, the most investigated delivery systems adopted for β-carotene can primarily be categorized into two groups: polymer-based delivery systems (PBDSs) and lipid-based delivery systems (LBDSs).

2.1. Polymer-Based Delivery Systems

Polymer-based delivery systems use the intrinsic diversity of polymers to develop encapsulating bioactive compounds in nanodelivery with improved functionalities. The long-term health risks of PBDSs either fabricated with a synthetic polymer or made up of natural polymers, such as proteins and carbohydrates, are regarded as minimal. However, the latter are either hard to scale-up as they require several heat and often complex treatments which are hard to control or result in porous micro-/nanoparticles, thereby not achieving the objective of encapsulation. A range of PBDSs have been reported in the literature. In the present entry, researchers have included only those PBDSs which are derived from either natural food grade materials or are generally recognized as safe polymers. Typical PBDSs include nano-/microspheres, nano-/microcapsules, hydrogel micelles, colloidal nano-/microemulsions and nanofibers, all of which mainly consist of synthetic or natural polymers (**Figure 1**A,B).

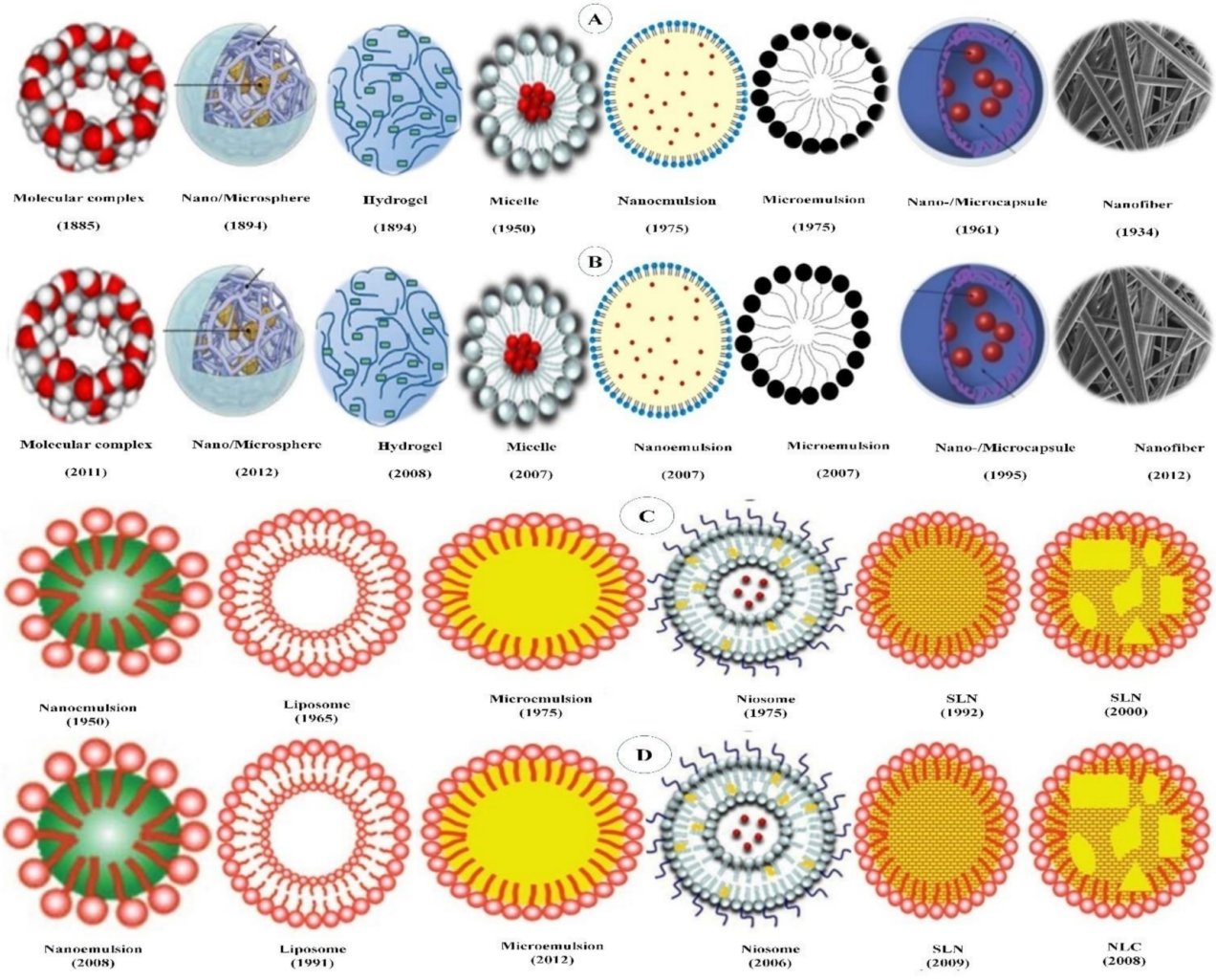

Figure 1. (**A**) Historical event in the evolution of polymer-based delivery systems; (**B**) historical event in the application of polymer-based delivery system for encapsulating β-carotene; (**C**) historical event in the evolution of lipid-based delivery systems; (**D**) historical event for applying lipid-based delivery system for encapsulating β-carotene.

2.2. Lipid-Based Delivery Systems

Lipid-based delivery systems (LBDSs) involve delivery systems which are principally composed of physiological lipid analogs such as surfactants as stabilizers (**Figure 1**A,B). LBDSs have been recognized for their promising biocompatibility, competency in GIT penetration, easy to scale-up and broad application [33][36]. LBDSs have been admired for their potential for drug delivery through various administration routes, particularly for the oral delivery of lipophilic

drugs, because of their competence to mimic the food lipids during the digestive process [37][38]. With their properties, lipid-based delivery systems offer an array of advantages over polymer-based systems as shown in **Table 1**. Some of these advantages of lipid-based nanodelivery systems entail: (i) biocompatibility and use of nontoxic excipients [36][39]; (ii) high drug payload [40]; (iii) viability of incorporating both lipophilic and hydrophilic bioactives [36]; (iv) prospect of controlled release and drug targeting; (v) improved drug stability [41]; (vi) averting of organic solvents [42]; (vii) cost-effectiveness [43]; (viii) ease of scale-up during production and sterilization [44]. Over the course of time, a range of lipid-based delivery systems have been developed for encapsulating bioactive compounds such as micelles, micro- and nanoemulsions, liposomes, niosomes, solid lipid carriers, nanostructured lipid carriers, bilosomes, cubosomes, etc. [45]. However, in the present entry, the emphasis has given those LBDSs which have been adopted for encapsulation β-carotene are discussed in the following sections.

Table 1. Various factors that need to be considered prior to selecting a delivery system for encapsulating any bioactive agent.

ENMS	Class of DeliverySystem	Subclass of Delivery System	Ability to Deliver Lipophilic and Lipophobic BA	Physical Stability	Biological Stability	Biocompatibility	Drug Targeting	Drug Loading	Feasibility to be Delivery System for β-Carotene
Lipid-derived delivery system	Self-assembled delivery system	Liposome	Yes	poor	Poor	Good	Moderate	Low to moderate	Poor
		Niosome	Yes	moderate	Poor	Moderate	Moderate	Moderate	Poor
	Particulate	Solid lipid nanoparticles	Only lipophilic	Good	Moderate	Good	Moderate	Moderate	Moderate
		Nanostructured lipid carriers	Only lipophilic	Good	High	Good	Moderate	High	Good
	Emulsion	Microemulsion	Yes	Moderate	Moderate	Good	Poor	High	Good
		Nanoemulsion	Yes	poor	Moderate	Good	Poor	High	Poor
	Self-assembled delivery system	Starch-based Micelle	Yes	Good	Good	Moderate	Poor	Poor	Good
		Protein-based micelles	Yes	Poor	Good	Moderate	Moderate	Poor	Good
		Carbohydrate							Poor
		Hydrogel	Yes	Good	Good	Poor	Poor	Poor	Good
		Colloidal nanoemulsion	Yes	Moderate	Moderate	Good	Poor	High	moderate
Polymer-derived delivery system		Nanoemulsion	Yes	poor	Moderate	Good	Poor	High	Poor
		Molecular complexes	Only lipophilic	Good	Moderate	Poor	Poor	Low	Poor
	Particulate	Protein inclusion complexes	Yes	Good	Moderate	Moderate	Moderate	Low	Poor
		Nanosphere	Yes	Good	Moderate	Moderate	Moderate	Moderate	Poor
		Microsphere	Yes	Good	Moderate	Moderate	Moderate	Low	Moderate
	Fibrous	Nanofiber	Yes	Good	Moderate	Moderate	Moderate	Low	Poor
	Capsular	Microcapsule	Yes	Good	Moderate	Moderate	Moderate	Low	Poor
		Nanosphere	Yes	Good	Moderate	Moderate	Moderate	Moderate	Poor

3. Safety Compliance and Risks of β-Carotene Nanoparticles

The customized properties of the discussed delivery systems, including the potential for bioavailability, better absorption and controlled release kinetics of the encapsulated bioactive compounds, may also impart unseen risks to biological systems [43][46]. It is assumed that utilization of biodegradable or natural materials may curtail the health hazards as compared to polymeric nanoparticles which are either derived from synthetic polymers or involve toxic organic solvents during their fabrication processes [46]. Due to the ambiguity on long- or short-term effects of direct or indirect employed nanoparticles in food systems, it is paramount to evaluate the impacts of nanoparticles on human health [47]. With regard to food safety, the FDA has listed certain strategies in conjunction with nanoparticle-based food and food components for

mass production [48]. Regardless of the potential health concern, at present no standardized legislation for incorporation of nanoparticles in food systems, particularly for nanoparticles encapsulating β-carotene, are available. Nevertheless, several agencies and governmental bodies insist that people embrace the safety concerns of nanoparticle-based food products in legislative guidelines [49]. The European Food Safety Authority (EFSA) has published an excellent report on the topic (https://www.efsa.europa.eu/en/efsajournal/pub/5327, accessed on 20 December 2020). This guideline provides an overview on the required information about physico-chemical characterization and the other data requirements. It also states about the performance of risk assessment of nanomaterials in the food and feed area including novel food, FCMs, food/feed additives and pesticides. This lack of universal legislations compelled duty-bound policymakers to outline a guideline specifically dealing with the nanoscale materials in the food system [50].

The potentially tailored bioavailability of encapsulated bioactive compounds in delivery systems is a key safety concern, specifically for bioactive compounds, or the nanodelivery systems which may become toxic beyond a certain dose. To scrutinize the safety aspects, the bioavailability of bioactive compounds needs to be revaluated when it is encapsulated within nanodelivery vehicles, and reflections on alterations of the Recommended Daily Allowance (RDA) as well as the Tolerable Upper Intake Level (UL) of encapsulated bioactives are needed [51].

In addition, food scientists may also need to conduct studies addressing the safety concerns associated with nanoparticles, with special attention regarding: (i) the physiochemical characterization constraints of nanoparticles utilized in food items such as food additives, enzymes, flavorings, food contact materials (FCMs), novel foods, feed additives and pesticides [52]; (ii) development of the testing strategies to determine and characterize hazards transmitted via the engineered nanomaterials (ENMs)—i.e., assays for in vitro genotoxicity, absorption, distribution, metabolism and excretion and repeated-dose trials to study toxicity in test animals such as rodents [53].

In addition, the interactions between food items and nanodelivery systems should also be debated, which may result in producing radical oxygen species, photoreactions, etc. In December 2014, EU legislative bodies have insisted that food industries mention relevant information on the label if nano-food products are sold [50]. According to this guideline, particles have one or more dimensions of either 100 nm or less and agglomerates above 100 nm exhibiting ENM characteristics and should be considered as ENMs. In conjunction with this, the FDA has drafted guidelines which clearly define ENM-derived foods as (i) agents or products having particle sizes within the range of 1 to 100 nm with at least one dimension being within the nanoscale; (ii) agents or products exerting biological, chemical and physical characteristic associated with nanoscale materials and that are also on the nanoscale even though they are not nanosized.

In addition to legislative guidelines, there are several moral responsibilities of the food processing manufacturers, including: (i) evaluation of the changes imparted on the food materials—i.e., impurities and physiochemical properties; (ii) evaluation of the safety of food materials after modifications; (iii) submission of the regulatory assessment reporting to the legislative bodies such as FDA, FSSAI, EU, FASSAI, etc.; (iv) identification and a statement about the regulatory concern due to the ingestion of the nanoparticle-derived food items.

Apart from the US-FDA, several other regulatory authorities from various countries including Australia, New Zealand (FSANS) and Korea (MFDS) have issued their own guidelines [54]. These agencies counseled to conduct safety experiments (in vitro as well as in vivo) to evaluate the effect of nanoparticle-containing foods and publish the data, as well as to establish guidelines before releasing these nanoparticle containing foods to the food supply chain. Nevertheless, there is a lack of specific guidelines regarding nanoparticles containing foods, thus it is high time that the legislative bodies should come together to frame a more universal guideline for nanomaterial-derived food products which can then be applied or further tailored to different countries.

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