β-Carotene within Loaded Delivery Systems

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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. This research area has rapidly evolved, with a plethora of innovative nanoengineered materials now being in use, including micelles, nano/microemulsions, liposomes, niosomes, solidlipid nanoparticles, nanostructured lipids and nanostructured carriers. These nanodelivery systems make conventional delivery systems appear archaic and promise better solubilization, protection during processing, improved shelf-life, higher bioavailability as well as controlled and targeted release.

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].

2. 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 ($OH^{\bullet}$) 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].

3. 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.

4. Challenges Associated with β-Carotene Food Fortification

β-Carotene is naturally found in various foods and is also commonly used as a natural pigment in food, pharmaceutical and cosmetic industries. This lipophilic molecule is characterized by the presence of a polyene structure with 11 conjugated double bonds with two β-ionone rings. Under environmental stress (temperature, humidity, pH, ionic strength and radiation), β-carotene may undergo transformation, resulting in the formation of different isomers such as 15-*cis*-β-carotene, 13-*cis*-β-carotene and 9-*cis*-β-carotene and several *trans*-β-carotenes [33][34]. *Cis*-isomers have bent structures and are likely to be more readily solubilized and adsorbed compared to *trans*-β-carotene which possesses a linear and rigid structure and has a high tendency to crystallize and aggregate as compare to the *cis*-isomers [35][36]. The unsaturated structure makes β-carotene prone to oxidation, resulting in the loss of its vitamin A functionality. Furthermore, β-carotene is also susceptible to isomerization when confronted with acidic conditions, high-salt, temperature, metal ions, peroxides and radiation during food processing and storage before consumption [36]. In addition, naturally occurring β-carotene is often complexed with protein molecules which limit its solubility and distribution in the food matrix, as well as its adsorption in human body [37].

Currently, β-carotene is one of the most exploited carotenoids and is usedto develop functional foods [38], formulate pharmaceutical supplements and prepare cosmetic products. However, food fortification, i.e., incorporating β-carotene within functional foods, is recognized as the most natural, appropriate and safe methods as compared to other drug administration routes including intravenous, intramuscular and subcutaneous ones [39]. However, within these functional food products, β-carotene is prone to physicochemical degradation during the production, processing and storage before food consumption. These limiting factors, in addition to its low bioavailability within the human gastrointestinal tract, make β-carotene difficult to incorporate into the food matrix and hence significantly impact its efficacy as a health beneficial plant compound.

Nanotechnology seems to be a logical solution to address these limiting factors, as it has demonstrated its potential to encapsulate, protect and delivery bioactive compounds using several delivery systems to improve their physicochemical stability, solubility, dispersibility and bioavailability upon ingestion [40][41][42][43][44]. Researchers have nanoengineered various kinds of delivery systems, such as microemulsion, liposomes, solid lipid carriers, nanostructured lipid carriers, nanocapsules and nanospheres to encapsulate and deliver bioactive compounds. These delivery systems are capable of improving stability, dispersity and bioavailability of bioactive compounds within the target food matrix. Although several excellent reports have already been published emphasizing the factors affecting the chemical stability of carotenoids [45], encapsulation techniques to protect them against environmental stress [46], production methods to prepare nanoengineered delivery systems [47] and delivery systems to improve their solubility or bioavailability [48], there is lack of reviews regarding β-carotene delivery systems, in particular with food applications.

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