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Review

Microencapsulation of vitamin A: A review

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ABSTRACT

Background: Vitamin A deficiency is recognized as a public health problem in a large number of countries. It mainly affects young children and pregnant women in low-income countries in Africa and South-East Asia regions (World Health Organization data).
Vitamin A is a fat-soluble vitamin and an essential nutrient provided to the human body in form of carotenoids (provitamin A) and retinol or retinyl esters (preformed vitamin A). The inadequate intake of this micronutrient through the diet may compromise a large spectrum of biological functions, namely vision, growth and development, immunological activity, reproduction and cellular growth and differentiation. The preparation of functional food and enteral formulas arises as a solution to provide to the individuals the partial or complete vitamin A nutritional requirements.
Scope and approach: Due to the properties of vitamin A and other retinoids these compounds have been used for several pharmaceutical and cosmetic formulations. However, the poor solubility in water and chemical instability of vitamin A can lead to its degradation during processing and storage. Microencapsulation may promote the stabilization of vitamin A in certain conditions and may improve a controlled release.
Key findings and conclusions: The present work starts with a reference to several topics of vitamins A. General aspects about microencapsulation are presented, as well as the reasons to apply this technology to vitamin A. The main encapsulating methods (the principles and main considerations) and encapsulating agents applied to this micronutrient are also discussed. The final section focuses on vitamin A release studies and its kinetics.

1. Introduction

The importance of vitamin A for vision health dates back to ancient Egypt as early as 1500 BC. At that time and according to the papyrus Ebers, patients who suffered from vision reduction in semi darkness conditions (nyctalopia or night blindness disease) were cured by topical application of liver juice or ox liver extract (previously cooked) in the eye (Ebell, 1937; Wolf, 1978, 1996). About this procedure, Wolf (1978) suggested that the droplets of liver oil, which is rich in vitamin A (retinol), entered the lachrymal duct where they were absorbed into the blood circulation and finally reached the retina. Currently the role of vitamin A in the visual process is well known (Dowling & Wald, 1958; Wald, 1955, 1968) and it is directly related to the rod cells present in retina of the eye. These cells are light-receptors that are responsible to enable us to distinguish between light and dark and contain the visual pigment rhodopsin. Rhodopsin is composed by 11-cis-retinal, an isomer of retinal (an aldehyde obtained by oxidation of retinol), and by opsin, the light-sensitive receptor protein. The exposure of rod cells to the light leads to rhodopsin destruction by bleaching, occurring the conversion of light into an electrical signal that is sent to the brain, resulting in the vision. According to this process it is important to ensure the continuous replacement of vitamin A constituent of rhodopsin to prevent vision impairment. In fact, rhodopsin works under low-light promoting dark adaptation.

Night blindness can be the first sign of xerophthalmia, warning to a severe vitamin A deficiency (Sommer, 1998, 2001). The following stages of xerophthalmia include conjunctival xerosis (on the conjunctival surface, mainly adjacent to the temporal side of the cornea, dry patches of keratinized epithelium appear) (Sommer, 2001), Bitot's spots (appearance of foamy or cheesy white accumulations of keratinized squamous epithelium and observation of an overgrowth of gram negative rods) (Sommer, Green, & Kenyon, 1981), corneal xerosis (the cornea loses its normal sheen and clarity due to corneal epithelium keratinized) (Sommer, 1998, 2001),

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corneal ulceration (Sommer & West, 1996), corneal necrosis (keratomalacia) (Sommer, 1998), and blindness (Sommer, 2001; Sommer & West, 1996). World Health Organization (2009) reports the results of collaboration work between Micronutrient Initiative and UNICEF, and Tulane University, which allowed them to estimate that in year 2000 about 7 million preschool-age children had night blindness and Bitot's spots. Additionally, the West (2002) work estimated for the same year that 19.8 million pregnant women had low vitamin A levels (serum retinol or breast milk concentrations < 1.05 μmol L^{-1}) and, from those, about 6.2 million suffered of gestational night blindness. The last referred estimation also enabled to understand that approximately two-thirds of the world's night blindness women lived in South and South-East Asia.

The importance of vitamin A goes beyond the vision health. This micronutrient, more precisely retinoic acid (a carboxylic acid which results of further irreversible oxidation of retinal) (Dowling & Wald, 1960) plays an important key role in reproduction, embryonic development, cellular growth and differentiation, maintenance of epithelial cellular integrity and immune function. As consequence, an insufficient ingestion of vitamin A can lead to spermatogenesis commitment/anomalies' (Mason, 1933; Wolbach & Howe, 1925) and reproduction failure before implantation (Evans, 1928), fetal development commitment (malformation of tissues and organs) (Dickman, Thaller, & Smith, 1997; Hale, 1933; Kaiser, Merrill, Stein, Breburda, & Clagett-Dame, 2003; Warkany & Roth, 1948; Warkany & Schraffenberger, 1946; White, Highland, & Clagett-Dame, 2000; White, Highland, Kaiser, & Clagett-Dame, 2000; White et al., 1998; Wilson & Warkany, 1948), disturbed cellular differentiation (Sommer, 2001, 2008), slowed growth and development (Bloch, 1931), impaired immunological function (Ross, 2012), anemia (Sommer & Davidson, 2002), infections (*i.e.* measles) (Ellison, 1932; Green & Mellanby, 1928; Green, Pindar, Davis, & Mellanby, 1931), and morbidity and mortality (Sommer, 2001).

Vitamin A deficiency is recognized as a public health problem in more than half of world countries and mainly affects individuals from poor societies and developing countries (WHO, 2009). The application of the adequate treatment can reduce the risk of development of complications related to vitamin A deficiency. These may include skin disorders (psoriasis and acne) (Sauvant, Cansell, Sassi, & Atgié, 2012), psychiatric pathologies (schizophrenia and Alzheimer's disease) (Olson & Mello, 2010) and certain cancers (Olson & Mello, 2010), among others (Sommer, 2001).

Prevention of vitamin A deficiency has been carried out by food fortification (functional food) (Dary & Mora, 2002) and enteral formulas prepared to provide complete or supplemental nutritional support to individuals (Fávaro, Iha, Mazzi, Fávaro, & Bianchi, 2011). In developed countries the overconsumption of these products is often associated to the toxicity of vitamin A (Dary & Mora, 2002). Therefore, the current market of vitamin A covers the food and pharmaceutical industries. Moreover, a review about the effect of this micronutrient on anti-aging treatment (Mukherjee et al., 2006) also shows the application of vitamin A in the cosmetic industry. However, vitamin A is poorly water soluble and highly unstable in the presence of oxidants, light, heat, temperature and moisture, among others (Gonnet, Lethuaut, & Boury, 2010; Teleki, Hitzfeld, & Eggersdorfer, 2013). Microencapsulation has been explored in order to overcome these limitations. In addition it is also an effective technique of controlled release of vitamin A (Donhowe, Flores, Kerr, Wicker, & Kong, 2014).

This review highlights an overall discussion about structure and historical perspective of sources, metabolism, microencapsulation (its importance, techniques and encapsulating agents) and release studies of vitamin A, and its kinetics.

2. Structure and historical perspective of vitamin A

Vitamin A is a term used to designate retinol and its natural derivatives with the same biological activity, namely retinal and retinoic acid (Blomhoff & Blomhoff, 2006). Retinyl esters, the storage form of retinol, and carotenoids are also considered vitamin A (Chapman, 2012; Mukherjee et al., 2006). Retinol (or all-trans-retinol) is a molecule with a cyclohexenyl ring linked to a side chain with four double bonds (all in trans configuration) and with an alcohol end group (Mukherjee et al., 2006). The oxidation of alcohol end group results in the formation of retinal or all-trans retinaldehyde, which can be further oxidized to all-trans retinoic acid (Mukherjee et al., 2006) (Fig. 1).

Experiments of McCollum and Davis (1913) enabled the first description of vitamin A. They reported that rats fed for several months with purified rations composed of pure casein, carbohydrates (in some rations a part of the carbohydrates was replaced by lard) and salt mixtures could restore their growth when diet was supplemented by ether extract of egg or of butter. This essential compound that naturally occurs in this type of food was named “fat soluble A” (later called vitamin A (Drummond & Coward, 1920)), as opposed to other accessory dietary factors called “water soluble B” (McCollum & Davis, 1915). At the same time, similar experiments were performed by Osborne and Mendel (1913) who observed the rats' growth when their diet was supplemented with evaporated whole-milk powder. Hence, Osborne and Mendel realized that milk contained something other than protein that was necessary for the growth of animals. Steenbock (1919) observed that “fat soluble A” obtained from butter, egg yolk and carrots presented the yellow color, probably due to the association of a yellow pigment (known today as β-carotene) (Steenbock & Gross, 1920). Furthermore, Steenbock speculated about the possibility of converting this factor

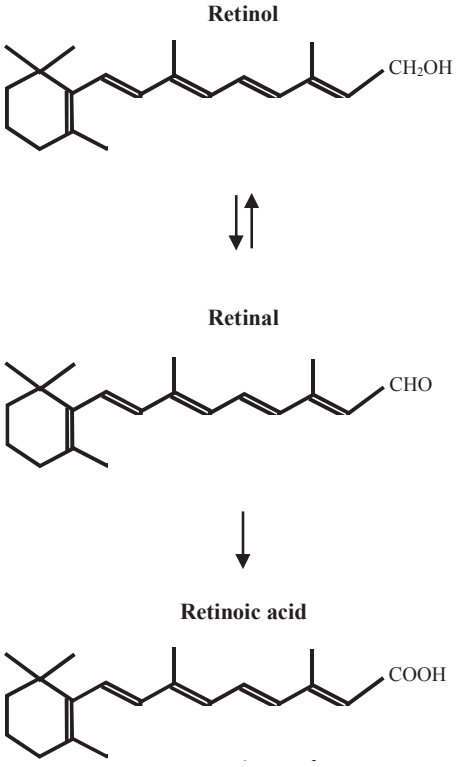

Fig. 1. Interconversion between vitamin A structures.
Adapted from Clagett-Dame and Knutson (2011), Heller and Shiffman (1985) and Mukherjee et al. (2006).