Oral Carotenoid Delivery: Role of Nanocarrier Systems

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***Abstract*—Carotenoids-apolar tetraterpenoid pigments that are commonly understood to exhibit broad-ranging beneficial systemic antioxidant, anti-inflammatory and maculoprotective effects-are profoundly hindered from serving as efficacious functional foods, nutraceuticals or oral medicines by low intrinsic oral bioavailability (F). Inefficient absorption follows: high solid-state crystalline stability; marked lipophilicity; vulnerability to digestive temperature-driven and oxidative catabolism in the digestive tract; and failure to undergo effective micellization in the lumen of the small intestine. In a systematic effort to circumnavigate these formidable physicochemical hurdles, nano-engineered delivery systems, especially lipo-based nanoarchitectures (nanoemulsions; solid lipid nanoparticles; nanostructured lipid carriers) and biopolymeric nanoparticle-based platforms, have been extensively developed.**

With these nanovectors, carotenoid bio-accessibility is improved: the lipophilic molecules are entrapped within protective nano-matrices, the rate of delivery to the enzymes of pancreatic lipolysis is augmented, and in turn their solubilized contents are provided for preferential uptake via apically disposed enterocyte membrane transporters SR-BI, CD36, and NPC1L1. This review systematically summarises physical constraints influencing carotenoid oral uptake and explains the mechanisms behind engineered lipo-based and biopolymeric nanocarriers. It critiques the standardised in vitro digestion model INFOGEST and discusses factors for industrial, toxicology, and regulatory progression.

***Index Terms*—Oral Bioavailability, Carotenoids, Nanocarriers, Nanoemulsions**

I. Introduction

The structurally heterogeneous, fat-soluble tetraperpenoids that occur in photosynthetic organisms as well as bacteria and fungi are known as carotenoids. In human health, they act, as systemic antioxidants, anti-inflammatory and maculoprotective agents and regulators of the organism's metabolism [1,2]. The dietary intake of the provitamin A carotenoids, viz. β-carotene, α-carotene and β-cryptoxanthin and non-provitamin A carotenoids: lycopene, lutein and zeaxanthin, and astaxanthin, may contribute to human health and well-being with demonstrated functions as outlined above however their functional benefit from application of oral carotenoid supplementation to functional foods and nutraceutical formulas is hampered by very poor bioaccessibility and oral bioavailability [3,4].

At their core, the greatest barrier to carotenoid absorption rests in their fundamental molecular characteristics: large, extensively conjugated polyene hydrocarbon backbone yielding significant hydrophobic character (log P>6-15), thermal and oxidative liability, and propensity for formation of closely packed, crystalline structures in plant chromoplasts. [5] As a result, nonprocessed or crystalline ingested carotenoids pass the upper GI largely unabsorbed, are not absorbed into the lower colon, or (more likely)

are locally decomposed while in the body before crossing the mucosal barrier. Nanocarrier architectures engineered to overcome these physio- and biochemical liabilities provide the chief avenue of delivery [6,7] . The subsequent review details the physical limitations of carotenoid delivery, intestinal transport mechanism(s), characteristics of lipid-, and polymer-nanocarrier systems, standardized in vitro digestion procedures, and clinical application directions [8].

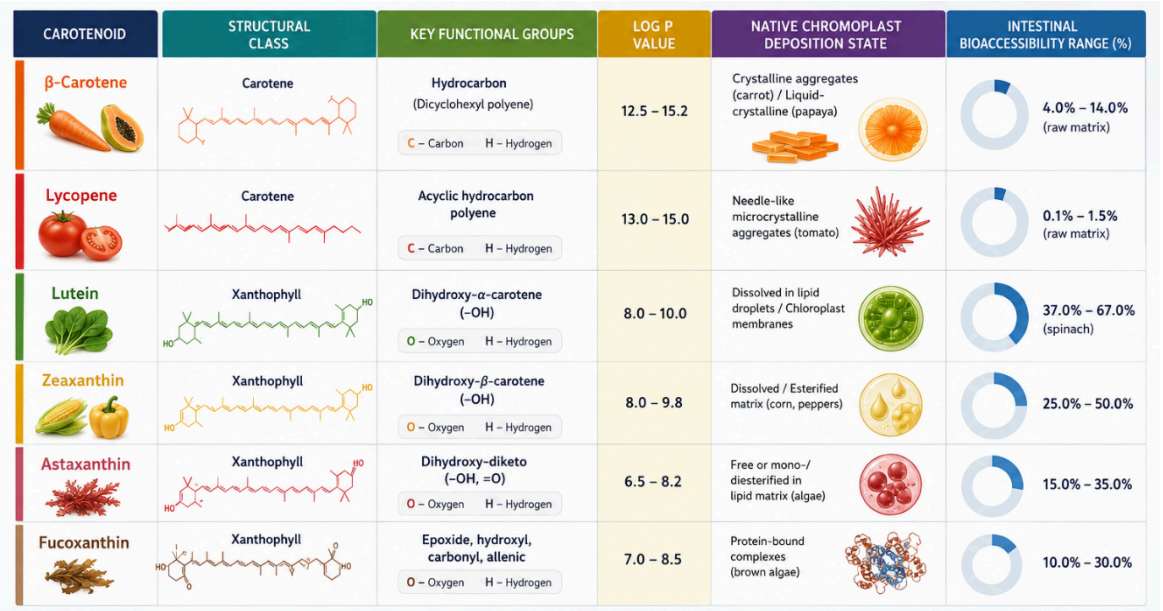

Figure 1: Physicochemical characteristics, chromoplast deposition states, and baseline intestinal bioaccessibility ranges of representative dietary carotenes and xanthophylls prior to nanoformulation.

Broadly speaking, carotenoids are separated into two significant structural categories based on their degree of oxygenation, non-polar carotenes (which only contain carbon and hydrogen atoms) and oxygenated xanthophylls (to which contain terminal functional groups: hydroxyl, keto, epoxide, or methoxy). This seemingly minute chemical distinction gives rise to a significant variation between the arrangement of molecules in the solid-state, the phase properties of individual molecules within lipid droplets and, importantly, the partitioning potential during transit of the food mass through the digestive tract [9,10].

The oral bioavailability (F) of a hydrophobic bioactive molecule is governed by the multi-step digestive sequence defined as:

$$F = F_B \times F_A \times F_M$$

where F_B is the fraction released from the food matrix and solubilized in intestinal mixed micelles (bioaccessibility), F_A is the fraction absorbed across the intestinal enterocyte apical membrane (cellular uptake), and F_M is the fraction escaping pre-systemic metabolism and reaching circulation intact [11].

When the carotenoids are free (unformulated), FB is the overall rate-limiting step. Most of native carotenes exist as all-trans stereoisomers which are rigidly structured and crystallized into crystal lattices with higher melting points in plastids of plants [12]. The structures can not be digested in the gastric medium or associate readily with pancreatic lipases, which are the enzyme that hydrolyse dietary lipids. Carotenes have no polar functional groups and are located in the interior of the lipid droplet in digesta. This causes poor access to the polar shell (including bile salt-phospholipid micelle interface), which contributes to very low bioaccessibility of 0.1 to 1.5 % for raw lycopene and 4 % for raw β-carotene [13].

Compared to carotenes and xanthophylls were remarkably more bioavailable (37–67%). The polar oxygenated groups also made xanthophylls less lipophilic than carotenes and shifted xanthophyll orientations so that they moved to the lipid-water interface during lipolytic processes in the digestive tract so that they could pass through to mixed micelles faster [14,15]. Nevertheless, both kinds of solubilised carotenoids are extremely fragile toward chemical breakdown through thermal isomerization and oxidation by free radicals along the conjugated polyene backbone by factors such as low stomach pH, dissolved oxygen and digestive enzymes, and they are fragile toward chemical changes.

II. Physiological Mechanisms of Intestinal Carotenoid Absorption

The solubilization of carotenoids, after consumption, necessitates disruption of the supramolecular food matrix by mastication and the shear forces present in the stomach. In the stomach, the carotenoids are solubilized in pre-existing dietary triglycerides consumed in the same meal. Once in the duodenum, pancreatic lipase, along with colipase, leads to triglyceride hydrolysis into sn-2-MAGs and FFAs [16]. These products of fat digestion (together with endogenous bile salts and phospholipids) self-assemble into spherical mixed micelles (3-10 nm diameter) and vesicles; micellar absorption is a necessary condition for trans-enterocyte carotenoid transport through the UAL of the enterocyte brush border. Until very recently, transepithelial absorption of carotenoids was thought to be driven by passive diffusion; abundant molecular and biochemical evidence now indicates that at physiological concentrations transepithelial absorption occurs mediated by membrane-embedded proteins from the scavenger receptor protein superfamily [17,18].

Table 1: Molecular pathway of intestinal carotenoid absorption. Following gastric emulsification and pancreatic lipolysis, carotenoids are incorporated into bile salt-phospholipid mixed micelles. Micelles permeate the unstirred aqueous layer to engage apical enterocyte transporters (SR-BI, CD36, NPC1L1). Intact carotenoids are assembled into chylomicrons and secreted into the lymphatic system, avoiding hepatic first-pass metabolism.

Factor	Target	echanism	Impact
SR-BI (SCARB1)	Provitamin A carotenes (β -carotene, α -carotene), Lycopene, Xanthophylls	Transmembrane glycoprotein that binds mixed micelles and facilitates hydrophobic bioactive transfer	Mediates saturable uptake; genetic single nucleotide polymorphisms (SNPs) directly modulate plasma response
CD36	β-Carotene, Lycopene, Lutein	High-affinity fatty acid translocase co-localized on apical enterocyte microvilli	Facilitates uptake of bulk lipophilic molecules; works synergistically with SR-BI
NPC1L1	Xanthophylls (Lutein, Zeaxanthin), α-/β -Carotene	Sterol transporter participating in clathrin-mediated endocytosis of lipophilic molecules	Inhibition by ezetimibe suppresses xanthophyll uptake; modulates selective sterol/carotenoid flux
LysoPC Content	Broad spectrum carotenoids	Cleavage product of phosphatidylcholine by pancreatic phospholipase A_2 (PLA_2)	Significantly enhances micellar membrane fluidity and boosts cellular uptake rates in enterocyte models

The absorption sequence is first based on the transport of mixed micelles carrying solubilised carotenoids across the unstirred aqueous layer toward the brush border membrane. At this level, carotenoids are proposed to be bound to a set of integral membrane proteins present in the apical membrane: Scavenger Receptor Class B type I (SR-BI); CD36 (cluster of differentiation 36) and Niemann-Pick C1-Like 1 (NPC1L1). Whereas binding affinity is strong with SR-BI and CD36 for hydrocarbon carotenes, binding affinity is higher with NPC1L1 and SR-BI for polar xanthophylls [19,20].

Simultaneously, the presence of lysoPC within the mixed micelle increases fluidity is increased and trans-epithelial transport of the carotenoids is greatly enhanced. Intracellular provitamin A carotenoids are enzymatically cleaved: beta-carotene 15,15'-oxygenase 1 (BCO1) is responsible for symmetric cleavage of beta-carotene to produce two molecules of retinal, which are then reduced to retinol and esterified into retinyl esters. Other intact carotenes (not provitamin A carotenes) may enter the cell and either undergo an asymmetric cleavage via beta-carotene 9',10'-oxygenase 2 (BCO2) generating apocarotenoids or get incorporated and then packaged into enterocyte chylomicrons that will not enter blood from enterocyte but instead will be secreted by basolateral exocytosis to transport cholesterol and carotenes, triacylglycerols and apolipoprotein B-48 toward the mesenteric lymphatic system: bypassing liver first-pass and then entering bloodstream to be released in tissues [21,22,23].

Unabsorbed carotenoids transit to the cecum and colon where they come into direct contact with intestinal microorganisms. Intestinal microorganisms metabolize them into low-molecular-weight apocarotenoids and volatiles. Carotenoids, in turn, act as prebiotics, increasing SCFA-producing gut microbes (e.g.,

Bacteroidetes and Firmicutes) and preserving intestinal mucosal barrier integrity [24,25]. Evolutionary considerations of the human homeostatic handling of carotenoids can be attributed to the mammalian dark time bottleneck with an all or none non-specific collection of non-polar pigments, such as β-carotene and lycopene, being collected into skin and fat tissues.

III. Lipid-Based and Polymeric Nanocarrier Delivery Architectures

Nanocarrier delivery systems can counteract poor micellarisation and degradation by designing them in such way that carotenoids are encapsulated in protective matrices of liquids or solids or even amphiphilic ones. These nanostructures enhance the effective surface area to volume ratio greatly, speeding up the lipolysis by overcoming the matrix release barriers. Furthermore, it does present the solubilized bioactives to the enterocyte transporters for entering into the enterocyte easily [25,26].

Nanoemulsions and Excipient Systems

Nanoemulsions are composed of sub-micron (10-500nm) oil droplets dispersed in water phase and are stabilized by an interfacial surfactant layer. The selection of carrier oil carbon chain length plays an important role in deciding post-digestion micellisation. Medium-chain triglycerides with MCFA (C_6-C_{12}) are rapidly digested by pancreatic lipase as there is very limited steric hindrance (no steric hindrance). But MCFA are dispersed into the water phase and cannot be carriers for a larger hydrophobic micelle domain size [27,28]. Long-chain fatty acids on the lipolysis of long-chain triglycerides (LCT, > C12 corn/palm/sun flower oil) join the BS to create expanding mixed micelles; thus the large hydrophobic domain is provided that can include bulky/highly lipophilic molecules like β-carotene, lycopene. Experimental formulation shows that β-carotene in LCT nanoemulsions showed more than two-fold enhanced bioaccessibility (25.2%) compared with that of MCT nanoemulsions (9.8%) [29].

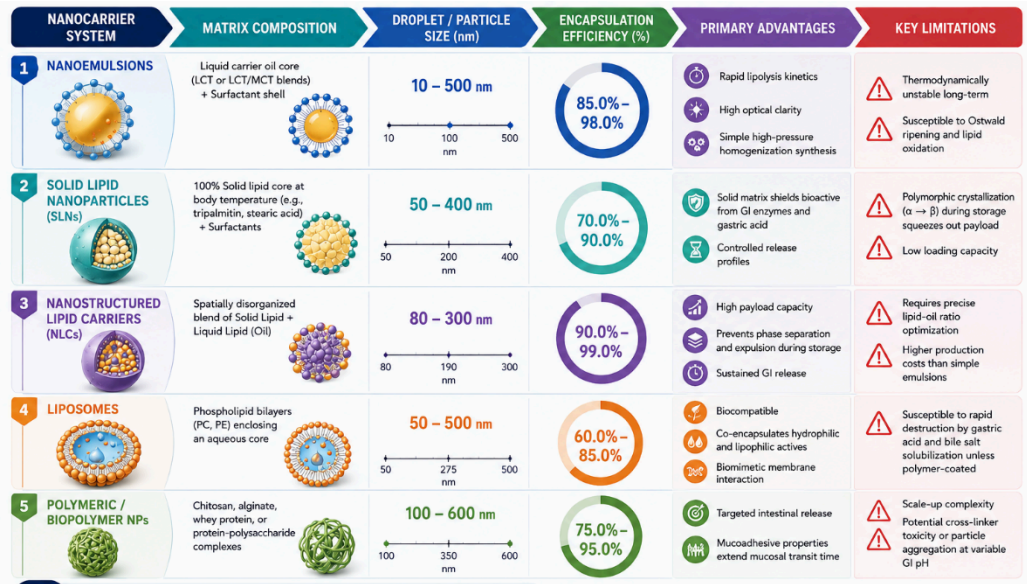

Figure 2: Architectural classification of nanoengineered carotenoid delivery systems. Liquid core nanoemulsions afford rapid digestion; NLCs incorporate spatial defects that prevent crystalline bioactive expulsion; biopolymer nanoparticles protect payloads from gastric acidity and prolong mucosal residence time via mucoadhesion.

Similar to emulsifier structure, emulsifier composition affects both interfacial lipolysis and gastrointestinal stability. The interfacial coverage of proteinaceous emulsifiers, e.g., whey protein isolate (WPI) and sodium caseinate (SC), is in the form of a viscous structure, giving more resistant effect toward gastric pepsinolysis and bile salt displacement compared with small-molecule synthetic non-ionic surfactants (i.e. Tween 20) or OSA-modified starches. When stabilize with sodium caseinate, sodium caseinate-stabilised nanoemulsion showed 28.8% and 12.0% of bioavailability and absorption in the intestine, respectively. In contrast, that result in Tween 20 is 13.8% and 5.0% [30].

Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

To overcome the chemical instability of liquid nanoemulsions, SLN has been developed. In SLN, the liquid oil phase is substituted by lipids that are solid at both ambient temperature and in body conditions at 37 °C such as tripalmitin, cetyl palmitate, steric acid. Three distribution models in SLN exist, solid solution model when the active ingredients are in molecule distribution within lipid phase, enriched shell model, at rapid solid state that active ingredient is accumulated into shell because of the lipid solidizing to a core at initial state. In the enriched core model that the bioactive precipitates into the nucleus before the surrounding shell solidifies. [31,32]

A major disadvantage of SLN is that Polymorphic transformation occurs upon storage time. With storage time and an increase in temperature, the polymorphic phase of lipid will change from the unstable phase α and β toward the stable crystalline form β [33]. As the structure become dense because of the tight crystalline the active ingredients carried molecule will squeeze out of the crystal lattice due to limited physical space, the matrix phase and the active ingredient phase will separate from each other, and the particles will aggregate [34] .

In overcome these problems second-generation NLCs were formulated by mixing lipids with different chemical structures - where the spatial mismatch of incompatible solid and liquid lipids (oils) would provide different ratios in range 70:30 to 99:1. The liquid lipid would prevent the perfect packing arrangement of solid lipid crystals which gave disordered and amorphous solid matrix composed of structural defects in the molecular structure where it accommodate relatively high concentrations of oil-soluble compounds such as non-polar carotenoids (carotenoids like β-carotene, lycopene, astaxanthin) which lead to encapsulation efficiency above 98% and preventing leakage of payload during the storage for the shelf life [35].

Vesicular and Biopolymeric Nanocarriers

Liposomes are Vesicles consisting of one or more concentric lipid bilayers encapsulating a hydrophilic aqueous environment. Extremely hydrophobic carotenoids are inserted into the lipid bilayer hydrocarbon tail environment. Though it possesses good biocompatibility, but unsecured liposomal vesicles are rapidly degraded by gastric acid, pepsin and detergents and bile salt action in the stomach. Coating the liposome with biopolymers like chitosan, pectin and alginate forms a protective electrostatic surface shield which retained structure integrity throughout the stomach and release the payload at the intestinal cavity. Similarly, biopolymer nanoparticles formed by ionic gelation (eg chitosan being cross-linked by TPP) effectively prevented thermolabile xanthophylls like astaxanthin from undergoing oxidative degradation and enhanced its stability and antioxidant power [36,37].

IV. Standardized In Vitro Digestion Dynamics and INFOGEST Models

Evaluating nanocarrier performance relies on standardized *in vitro* digestion models, most prominently the INFOGEST international consensus protocol. The INFOGEST framework simulates sequential oral, gastric, and small intestinal phases under controlled temperature ($37^{\circ}C$), pH, enzyme activity, and electrolyte concentrations [38].

In the intestinal phase, the rate of reaction of lipid digestion as generally analyzed by means of the pH-stat titration; this analyzed the amount of NaOH volume which neutralizes the free fatty acids released by pancreatic lipase. Carotenoid bioaccessibility (%) was measured by using ultracentrifugation, then RP-HPLC, and often a C30 stationary phases were specifically applied for analyzing the geo isomer (all-trans vs cis) [39] ;

$$Bioaccessibility\ (\%) = \left(\frac{C_{micelle}}{C_{initial}}\right) \times 100$$

where $C_{micelle}$ is the carotenoid concentration isolated within the clear aqueous micellar phase and $C_{initial}$ is the total concentration initially present in the formulation matrix.

Table 2: Standardized INFOGEST consensus in vitro digestion workflow for assessing carotenoid bioaccessibility.

Digestion Phase	Fluid & Enzymatic Composition	Operational pH & Duration	Primary Physicochemical Transformations
Oral Phase	Simulated Salivary Fluid (SSF), α -amylase, mucin	pH 7.0 ± 0.2; 2 min	Mastication simulation; droplet wetting; initial biopolymer degradation
Gastric Phase	Simulated Gastric Fluid (SGF), pepsin, gastric lipase	pH 3.0 ± 0.2; 120 min	Protein shell proteolysis; lipid droplet flocculation/coalescence; partial lipolysis ($10 - 30\%$)
Intestinal Phase	Simulated Intestinal Fluid	pH 7.0 ± 0.2; 120 min	Complete triglyceride hydrolysis; liberation of

	(SIF), pancreatin, bile salts, pancreatic lipase		FFAs and MAGs; mixed micelle assembly

The interfacial properties of nanocarriers result in modification of digestion kinetics due to altered physical mechanics [40]. Diminution of droplet size from $10\,\mu m$ to $100\,nm$ increased specific surface area (A=6ρd), enhancing rate of pancreatic lipase adsorption and rapid rate of lipid hydrolysis. Resultantly, fast production of FFAs and MAGs results in formation of mixed micelle quickly. On the contrary, extreme amount of surface area produces an abundance of FFA rapidly, competing for lipase binding sites without adequate bile salts or Ca2+ binding and sequestration of FFAs. Henceforth optimization of size depends on appropriate bile salt concentration [41,42].

V. Translational Challenges, Regulatory Frameworks, and Future Outlook

In terms of industrial processing scale-up, an approach utilising high-energy homogenization or microfluidization for nanocarrier production may lead to localized high shear stress which, accompanied by the local thermal energy input involved in high-pressure processing, induces thermomechanical breakdown and destabilization of the thermolabile polyene chain in carotenoids [43] . On the other hand, sub-100 nm radius nanoemulsion systems will experience increased Laplace pressures at room temperature. The high Laplace pressure contributes to high rates of Ostwald ripening and thus both phase separation and payload leakage as well as recrystallization, after prolonged storage [44].

From the toxicological point of view, the in vivo safety profile of artificial emulsifiers such as polysorbates and polyoxyethylene alkyl ethers is a critical barrier since large amounts of artificial surfactant interact with the plasma membrane of the enterocytes, degrade the tight junction integrity and cause localized enteritis at the gut mucosa, whereas unavoidable co-ingestion of inert inorganic nanoparticles (likeTiO_2 and artificial amorphous silica) affect the digestion parameters of lipids and unpredictable shifts at the gut microbial profile occur [45,46]. From a regulatory view, stringent evaluation requirements for novel foods and nanomedicine established by health agencies (e.g., U.S. FDA and EFSA) should be addressed. Standardized in vitro models such as INFOGEST would provide reproducible and relevant bioaccessibility values but miss specific parameters of human physiology, like intestinal peristalsis, the diffusion barrier posed by the mucus layer, gradients in transporter expression and constitutive enterocyte uptake kinetics. Elevated levels of in vitro micellarization would, hence, not correlate with increased in vivo oral bioavailability [47,48].

VI. Conclusions

Lipid- and polymer-based nanocarrier architectures overcome all these issues: Carotene type dictates structure choice: The relatively non-polar β-carotene and lycopene require LCT oil core architectures in formulations like nanoemulsions or NLCs to build swellable mixed micelles with high hydrophobic interior [49]. Conversely Polar xanthophylls like Lutein and astaxanthin use biopolymer matrices or a biopolymer-supported NLC core that maximizes interfacial capacity and chemical stability. Second-generation NLCs resolve challenges from polymorphic crystallization and payload expulsion from solid lipid nanoparticles (SLNs): second-generation NLCs (not a pure lipid matrix) improve Encapsulation efficiency (98%+) and long-term stability from problems presented by polymorphic crystallization, thereby enhancing in vivo cell uptake and stability. Protein surfactants are superior barriers than synthetic ones; Proteinaceous emulsifiers (whey protein isolate, Sodium caseinate) are preferred because of better protection from the stomach and enzymes resulting in increased cell uptake and safety profile, better than synthetic stabilizers; Priorities for clinical application: Moving from vitro INFOGEST models towards in-vivo bioactivity involves; establishing robust clinical safety methodologies and studies on its interaction with the gut microbiome, developing low-thermal processing/at low shearing stress methods suitable for scale-up.

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