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Review Article

A Critical Review on the Bioavailability Promotion of the Food Bioactive Compounds: Nano Lipid Carriers Perspective

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Abstract

Currently, a large number of people favor meals that are rich in nutraceuticals and phytochemical compounds, which help with the treatment or prevention of chronic diseases. Oral bioavailability is a crucial component of phytochemical bioefficiency, and endogenous mechanisms have a significant impact on how well nutraceuticals and phytochemicals are absorbed by the body. In addition to endogenous variables, exogenous factors that impact the bioavailability of bioactives include the food matrix, food processing, and food storage. Different delivery systems have evolved in this regard, and nanoscale delivery tools have also been created. Delivery methods that use nanostructured lipid carriers show benefits such as enhanced loading capacity, solubility, encapsulation effectiveness, storage stability, bioavailability, and half-life. They also provide safe food systems and regulated release. In this review, the outcomes of recent experimental reports are comprehensively reviewed. In addition, the food processing, storage, gut milieu circumstances, the release process from the food and nano delivery systems in the gastrointestinal tract (GIT) milieu, interactions with other GIT constituents, main delivery systems based on nanostructured lipid carriers for their encapsulation and eventually encapsulating technological barriers, food safety concerns, and regulatory issues of nutraceutical and phytochemical compounds are discussed.

Introduction

People are becoming more and more likely to favor meals that can meet their long-term well-being demands in addition to their nutritional requirements for the body's biological processes.[1] Because of this, people tend to like foods that are high in bioactive substances or nutraceuticals. These substances may lower the risk of both long-term and short-term diseases, such as cancer, obesity, neurodegenerative disorders, and immune system deficiencies.[2] De Felice and colleagues created the term "nutraceutical" to designate bioactive substances with nutritional and physiological benefits by fusing the words "nutrition" and "pharmaceutical".[3] Nutraceuticals are "foods or elements of foods delivering health advantages, such as the treatment and prevention of illnesses," according to De Felice's definition. Various nationalities have different definitions and uses for the term "nutraceutical". According to the description given previously, nutraceuticals also include elements that aren't often classified as nutrients (such as vitamins and minerals) or those the body can't produce on its own but are nonetheless proven to be good for human health. When seen from a chemical perspective, nutraceuticals are substances that fall into many classifications, such as carotenoids, alkaloids, terpenoids, conjugated linoleic acids (CLAs), polyunsaturated omega-3 fatty acids (PUFA omega 3), polyphenols, and so on.[4,5]

The usage of nutraceuticals and nutritional supplements has significantly expanded as a result of the major changes in people's lifestyles in industrialized nations. In this regard, it is crucial to establish precise and comprehensive rules about the effectiveness, safety, and toxicity of food

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supplements and nutraceuticals, respectively. The biological effectiveness of nutraceuticals ingested through natural resources, dietary supplements, and/or functional foods has therefore been the focus of academic and industrial study during the past ten years. According to evidence from the literature, the following themes are often studied by researchers in the disciplines of food, medicine, and pharmaceuticals: the development and standardization of in vitro and in vivo research approaches for the assessment of the processes underlying nutraceutical bioavailability; the diversification of food systems and nutraceutical delivery methods for boosting oral bioavailability; and the in vitro and in vivo screening of the physiological functions of nutraceuticals.[6]

With regard to bioactive compounds, they are widely distributed in roots, pulses, grains, vegetables, fruits, and other plant sources.[7] Multiple therapeutic effects and health promotion initiatives for the treatment and/or prevention of coronary heart, cardiovascular, urinary tract infections, degenerative and metabolic disorders, stomach lesions, and several types of tumors, as well as dental issues, have been demonstrated by epidemiological and clinical investigations of specific bioactive substances.[8,9] Natural bioactive substances, on the other hand, are chemically brittle and prone to oxidative deterioration, especially when exposed to heat, moisture, light, and oxygen.[10,11] The fortified product's phenolic constituents may deteriorate due to oxidative degradation, which might then produce free radicals, cause the creation of disagreeable tastes and aromas, and negatively impact the product's storage stability, sensory qualities, and customer acceptance.[12,13] Furthermore, due to their unique properties, such as quick discharge, poor solubility, low bioavailability, and ease of degradation in the context of environmental challenges, the use of pure bioactive chemicals (for example, phenolics) is particularly restricted in biological formulations.[14] Encapsulation is therefore seen as a workable alternative to maintain the integrity of bioactive substances or to improve their application to nutraceutical, food, or biological compositions. The two main methods of encapsulation technology are micro- and nano-encapsulation, both of which specialize in enhancing product functioning. The majority of investigations have demonstrated that improving the solubility of encapsulated bioactives, preventing their biochemical and chemical deterioration at pH variability or in the existence of enzymes and other elements of gastrointestinal tract (GIT) fluids, regulating discharge of bioactives, and improving uptake via the epithelial layer are all factors that contribute to their increased bioavailability.[15-17] Due to its unique characteristics, such as high encapsulation effectiveness and performance for loading, optimized consistency, consistent discharge pattern, and covering up unfavorable tastes, nanoencapsulation or the progression of nano-scale delivery methods for bioactive constituents has attracted significant interest recently1.[18,19]

Hence, in the current review, the outcomes of recent experimental reports are comprehensively reviewed, and the food processing, storage, and gut milieu circumstances, the release process from the food/nano delivery systems in the GIT milieu, interactions with other GIT constituents, main delivery systems based on nanostructured lipid carriers for their encapsulation and eventually encapsulating technological barriers, food safety concerns, and regulatory issues of nutraceuticals and bioactive compounds have been discussed.

Food Processing, Storage, and Gut Milieu Conditions

Foods are treated using mechanical (homogenization, cutting, and washing), thermal (freezing, boiling, drying, canning, pasteurization, evaporation, and blanching), chemical, or/and biological processes (enzymatic treatment, fermentation, esterification, hydrolysis, and salting) to emphasize the new qualities and lengthen the shelf life. Boiling and frying are other methods of preparing food. These processes alter the food matrix's physicochemical characteristics, such as denaturation of proteins, water and electrolyte loss, polysaccharide gelling, an increase or decrease in the number of antinutrients like phytates, and the breakdown of beneficial substances.[20,21] The sensory value of finished goods and the health advantages of food items for the human body are both impacted by the unfavorable breakdown of the bioactive elements in the food matrix.[22]

The chemical change of the biocomponents into hazardous chemicals with carcinogenic, mutagenic, and teratogenic consequences makes heat treatments the most severe food preservation method.[23] More contemporary eco-friendly preservation techniques, such as light pulses, pulsed electric field processing, and high-pressure processing, have indeed been established to lessen the detrimental impacts on the microstructure, sensory qualities, and nutritional features of foods. In addition to these methods, innovative approaches to food packaging have been created employing nanoparticles with antibacterial capabilities.[24] By preventing the loss of nutrients from the food matrix, avoiding their deterioration by exposure to air, moisture, and light, and inhibiting the development of microbes, nanomaterials used in active food packaging increase the bioavailability of nutrients.[25]

Different aspects of food processing have an impact on the bioaccessibility and bioavailability of bioactive elements. According to research, the nature of nutraceuticals, the arrangement and content of the food matrix, as well as the processing method, all affect the bioaccessibility and bioavailability of these compounds.[26,27] For instance, cutting plant-based meals (nuts, fruits, berries, seeds, and vegetables) might increase the bioavailability of nutraceuticals by rupturing the chloroplast or chromoplast cell walls, increasing the availability of the nutraceuticals.[28] Additionally, both moderate thermal pasteurization and moderate high-pressure pasteurization (HPPA) boosted the bioaccessibility of ω-carotene by causing a decrease in the stiffness of carrot tissue, but the moderate HPPA

generated a higher rise in the bioavailability due to differing physical consequences on the cellular morphology.[29]

Shi and Maguer (2000) investigated the impact of thermal treatment and found that the isomerization of all-trans types to cis isomers increased the bioavailability index of lycopene in heat-treated tomato goods compared to fresh tomatoes that had not been treated.[30] Over the past few decades, a great deal of research has been done on the impact of high-pressure processing (HPP) on the accessibility of carotenoids, vitamins, minerals, and other nutraceuticals from various food matrices.[25,31] Briones-Labarca and colleagues (2011) discovered that when apples were exposed to 500 MPa pressure for 2, 4, 8, and 10 minutes, their antioxidant capacity increased during the course of the digesting process, proving that HPP enhanced the release of antioxidant elements in the small intestine.[32] Other researchers have examined how HPP affects the bioavailability of amino acids, micro-compounds, and starch in brown rice that has been germinated.[33] According to in vitro assays, copper and calcium from germinated brown rice treated at pressures of 1.1 to 500 MPa for 10 min were two and ten times more bioaccessible than unprocessed products, respectively, but iron's bioavailability was reduced by two to three times. After the high-pressure treatment, the bioaccessibility of amino acids, notably γ-aminobutyric acid, and starch digestibility, both improved.

Numerous studies have also looked at how processing affects the phenolic compounds' bioaccessibility and bioavailability properties.[34,35] According to the results, processing plant-based products can lead to various alterations in the food's matrix that increase the bioaccessibility and bioavailability of polyphenols, such as the chemical conversion into more bioavailable types, weakening of connections between polyphenols and other matrix elements, reducing of phytate content through heat decomposition or fermentation, and the breakdown of plant cell walls.[35] The bioaccessibility of polyphenols varies depending on the matrix composition and cooking technique. In this way, boiling causes the carrots to completely lose their polyphenol content, but steaming and frying cause a smaller (30%–40%) loss. In both boiling and frying, broccoli and courgettes lost a significant proportion of their total phenolic content.[36]

Proteins can go through significant chemical changes during food preparation and storage that lower their nutritional value.[37] The presence of antinutrients in the food matrix or the formation of antinutrients by heat or alkaline treatment can alter the amino acid bioavailability and protein digestibility of food. Different food matrices include certain antinutrients that prevent the digestion of proteins, including cottonseeds (gossypol), cereals (phytates), and vegetables (trypsin and tannin inhibitors).[38] Based on Maillard and the racemization processes, antinutrients are created when food is heated or exposed to an alkaline environment. When protein-rich foodstuffs are heated up or stored, reducing sugars and lysine combine to form the Maillard reaction.[39] In addition to chemicals that enhance the fragrance, flavor, and color of cooked foods (such as roasted meat, bread, coffee, etc.), the Maillard reaction also creates undesirable substances that are regarded as off-flavors, such as those found in ultra-high temperature (UHT) processed milk. Paradoxically, the Maillard process also creates substances that prevent amino acid bioavailability and protein digestion. Fructose and lactuloselysine produced by the Maillard reactions at low temperatures are thereby converted into carbonyl derivatives at high temperatures, where they might interact with some other free amino acids produced by protein hydrolysis. Proteins' hydrophobicity and tertiary structure, in addition to their texturing capabilities, solubility, gelation, foaming, and emulsifying are altered by the Maillard process.[40]

Lysinoalanine (LAL) production and the racemization of L-amino acids to D-amino acids have been revealed to be two other significant processes that influence the bioavailability of amino acids and protein digestibility under heat or alkaline treatments.[38] Dehydroalanine residues and lysine amino groups react to generate LAL, which results in the loss of threonine, cysteine, and lysine as well as a reduction in the digestibility of proteins. LAL is a crucial factor in determining the degree of protein degradation in high-protein foodstuffs, particularly in newborn formulae. FAO/WHO advised using the Protein Digestibility-Corrected Amino Acid Score (PDCAAS) technique to assess the protein quality of foods. This approach is based on correcting for discrepancies in protein digestibility identified using a rat experiment by comparing the level of critical amino acids in the sample protein with the concentration of the same amino acids in a standard pattern.[41]

The physicochemical and physiological circumstances (surfactants, presence of enzymes, the chemical blend of the GIT fluids, pH, mechanical forces, etc.) to which the consumed foods are subjected throughout their transit through the GIT stages are referred to as the GIT factors that affect the bioavailability of nutraceuticals.[42] These variables may impact the solubility and release of nutraceuticals, as well as how they interact with other biocomponents in the GIT fluids and undergo chemical and biological changes. The elements that can have a significant impact on the pathways responsible for food digestion and the oral bioavailability of bioactive elements include age, genetic characteristics, and consumer health.[43] For instance, the composition of the gut microflora, the presence of specific chronic conditions in the kidneys or liver, the regular or suggested diet, the existence of specific GIT derangements (intestinal secretion, motility, gastric emptying speed, and gastric acidity), and so forth, all affect the bioavailability of nutraceuticals.[34] Newborns' GIT systems differ from those of adults in terms of pH, enzyme concentration, and activity. As a result, the gastrointestinal pH of infants is less acidic than that of adults. In the first three months, the stomach pH of infants is 3.0 to 4.0; after that, it drops to 1.5

to 3.0 until the age of one year.[44]

Nutraceuticals' Release Process from the Food/Nano Delivery Systems in the GIT Milieu

The bioavailability of nutraceuticals is significantly reduced by the discharge of such substances from food matrices or nanocarriers. The release regulated by the swelling procedure and the release regulated by the dissolving/erosion method are the typical strategies of bioactive discharge from protein- or polysaccharide-based hydrophilic polymer nanoparticles. The enzymatic activity on the biopolymer may potentially cause carrier erosion.[45] The connections between the polymer—bioactive elements—and water alter when bioactive-loaded nanocarriers are introduced into the GIT fluid. Water molecules get trapped between the polymer chains and cause the polymer to transform from the vitreous state to the elastic state. In these conditions, the gel layer thickness varies, which affects how quickly biocomponents discharge. Diffusion, swelling, and erosion all take place in quick succession after the water has entered the nanocarrier.

The hydrophilic bioactive substances dissolve and diffuse through the nanocarriers' walls as a result of coming into contact with water. The release of hydrophobic bioactives is more challenging to produce since they do not dissolve in water, which corresponds to a controlled erosion or breakdown of the polymer. Complex methods are followed for the discharge of hydrophilic bio-elements from nanocarriers, as explained by the mathematical designs.[46,47] According to Table 1, the release rate is influenced by the duration of food in the GIT phase, the morphology of the food matrices and the delivery method, the nutraceutical's physicochemical characteristics, and the circumstances of digestion (Table 1).

Table 1. Nutraceuticals' release from various food nanocarrier under *in vitro* circumstance.

Nutraceutical/ Bioactive compound	Type of nanocarriers	Materials for encapsulating	Condition of simulated gastric fluid	Releasing in simulated gastric fluid (%w/w)	Condition of simulated intestinal fluid	Releasing in simulated intestinal fluid (%w/w)	Ref.
Linoleic acid	–	Spring dextrin	pH 1.2 without enzymes, 3 hr	7%	pH 6.8 without enzymes, 3 hr	18%	48
Alfa-linolenic acid	–	Spring dextrin	pH 1.2 without enzymes, 3 h	18%	pH 6.8 without enzymes, 3 hr	22%	
Vitamin D_3	–	Carboxymethyl chitosam (CMCh); Soy protein isolate (SPI); CMCh/SPI 1:1	pH 1.5 without enzymes, 2 hr,	40%; 86.1%; 42.3%	pH 6.8 without enzymes, 3 hr	38%; 8%; 36%	49
	–	Whey protein isolate	pH 2.0 with enzymes, 2 hr	5.6%	pH 7.0 with enzymes, 2 hr	65.99%	
β-Carotene	–	Sodium caseinate	pH 2.0 with enzymes, 2 hr	89.6%	pH 7.0 with enzymes, 2 hr	71.3%	50
	–	Soybean protein isolate	pH 2.0 with enzymes, 2 hr	74.3%	pH 7.0 with enzymes, 2 hr	60.6%	
Gallic acid; Ascorbic acid; Quercetin; Curcumin	Noisome	Tween 60	pH 1, without enzymes, 2 h	8%; 27%; 12%; 30%	pH 7.4 without enzymes, 10 hr	28%; 41%; 42%; 63%	51
Curcumin	Polymer nanocarriers	Amidated low-methoxy pectin/ surfactant - Solutol - Transcutol - Caseinate	pH 1.2,without enzymes, 2 hr	4%; 0%; 0%	pH 6.4, without enzymes, 4 hr	98%; 85%; 85%	52
Curcumin/ Catechin	W/O/W double emulsions	Olive oil/PGPR	–	–	pH 7.2, without enzymes, 6 hr	Curcumin 40% to 50%; Catechin 80% to 90%	53
Folic acid	Biopolymeric nanocarriers	Zein	pH 1.2 With enzymes, 2 hr	–	pH 6.8 with enzymes, 10 hr	85%	54
Curcumin	O/W nanoemulsions	Emulsifiers: Whey protein concentrate; Tween 80; MCT-60	pH 1.5, with enzyme, 2 hr	5.48%	pH 6.8, with enzyme, 3 hr	77.75%	55

Table 1 Continued.

Vitamin D_3	O/W nanoemulsions	Medium-chain triglycerides (MCT); Corn oil; Fish oil; Orange oil; Mineral oil	–	–	–	Data for bioaccessibility: MCT 20%; Corn oil 84%; Fish oil 70%; Mineral oil 40%	56
Folic acid	–	Sodium caseinate	pH 1.2 with enzymes, 2 hr	~57%	pH 6.8 with enzymes, 10 hr	~85%	54
Chlorogenic acid	–	Alginate/modified tapioca starch	pH 2.3 with enzymes, 2 hr	20% to 60%	pH 6.8 with enzymes, 2 hr	7% to 15%	57
Riboflavin	Protein-nanoparticles	β-Lactoglobulin	pH 3, with enzymes, 2 hr	11%	pH 7.0 with enzymes, 6 hr	35% duodenum; 38% jejunum; 5% ileum	58
Vitamin D_3	Lipid nanocarriers	Capric and caprylic acid triglyceride (Labrafac); Soybean lecithin	pH 1.2 without enzymes, 2 hr	9.6%	pH 7.4 without enzymes, 6 hr	16.2%	59
Curcumin	O/W nanoemulsions O/W multilayer nanoemulsions (layer-by-layer [LBL])	MCT; SDS; Chitosan; Alginate	pH 2, without enzymes, 54 hr	Not released	pH 7.4, without enzymes, 54 hr	Data for bioaccessibility: O/W nanoemulsions 43.64%; O/W-LBL 26.98%	60
Fish oil	–	Alginate	pH 3 without enzymes,3 hr	10% to 15%	pH 6.8 without enzymes, 4 hr	80%	61
Vitamin D_3	W/O/W double emulsions	Soybean oil/ PGPR/sodium caseinate	pH 1.0, with enzyme, 30 min	0%	pH 7, with enzyme, 2 hr	10%	
Vitamin B_{12}	–	–	pH 3, with enzyme, 30 min	5% to 10%	pH 7, with enzyme, 2 hr	85% to 90%	62
β-Sitosterol	–	–	pH 1.0, with enzyme, 30 min	0%	pH 7, with enzyme, 2 hr	22%	
Curcumin	Pickering emulsion stabilized by nanoparticles	Chitosan/gum arabic	pH 1.2, with enzyme, 2 hr	0.30% nanoparticle 33%; 0.75% nanoparticle 40%	–	–	63
Ferulic acid	Resistant starch nanoparticles	Flax seed oil	pH 3, with enzyme, 1 hr	10%	pH 7.5, with enzyme, 3 hr	22%	64

Using both single-stage static GIT simulations and multi-stage static GIT simulations, McClements and his colleagues thoroughly investigated the changes that occur to lipid-based nanoparticles, notably nanoemulsions, as they transit through the GIT.[65] With most emulsions, the droplet charge was initially negative because the pH of the aqueous phase (pH 7.0) was above their isoelectric points, according to an analysis of the electrical characteristics of the droplets coated in different proteins. Droplets of the emulsions turned positive after moving through the simulated stomach fluid as a result of a pH reduction below the protein's isoelectric point.[66] Additionally, the adsorption of elements of intestinal fluid on the nanoparticle surface may have an impact on the interfacial characteristics of lipid nanoparticles. Competitive adsorption is when the adsorbed molecules join (co-adsorption) or replace the original molecules.[67] The discharge of hydrophobic nutraceuticals and the size of nanoparticles are both influenced by changes in electrokinetic potential values. Due to the increased interphase surface and interaction with lipolytic enzymes, the tiny size of nanoparticles causes a greater nutraceutical release rate. Additionally, nanoparticles' small size facilitates their adsorption across the epithelial cell layer. The processes of Ostwald ripening, coalescence, diffusion, and flocculation, which are affected by pH fluctuation, ionic strength, emulsifier nature, bile

salts, and dietary fiber, are what cause the rise in particle size.[68]

All stages of the GIT result in the release of nutraceuticals. Due to the brief length of residence, which is influenced by the food condition (liquid, semisolid, and solid), food viscosity, and temperature, the release rate in the oral cavity is minimal. The resulting particles are combined with saliva to create a cohesive bolus whose rheological characteristics enable swallowing. Mucin, which is found in gastric juice and saliva, is crucial to the lubrication and hydration of food. Mucin is indeed a negatively charged polyelectrolyte due to its chemical makeup (20% proteins and 80% oligosaccharides), taking into account the ionized carboxylic groups. Mucin has a negative charge and an electrokinetic potential of –15.4 mV at a pH of 7, which is considered neutral. The electrokinetic potential of mucin approaches zero (–0.9 mV) as pH declines from 7 to 2 due to a reduction in the quantity of ionized carboxylic groups.[69] When moving through the various GIT phases, these electrical characteristics have an impact on the integrity of polymer-coated nanocarriers packed with nutraceuticals.

Chang and McClements (2016) investigated the impact of mucin on sodium caseinate-stabilized emulsions and demonstrated that, in pH values between 6 and 7, the electrokinetic potential of the emulsion is unaffected by mucin due to repulsive encounters between the electrical charges of caseinate that are absorbed by the surface of oil droplets and its anions. The electrokinetic value of caseinate-stabilized emulsions, on the other hand, would be around +35 mV and –10 mV when mucin is absent and present, respectively, in the pH range of 4 to 2. This is a result of the mucin anions' affinity to the positive ions of caseinate.[69] Qin and colleagues (2017), who investigated the digestive process of emulsions stabilized via β-lactoglobulin, sodium alginate, and chitosan, obtained similar findings.[65] Proteins and polysaccharides are being employed in the preparation of nutraceutical-loaded biopolymeric nanoparticles, and their capacity to regulate the site of nutraceutical discharge is dependent on their chemical structure.[70,71] In contrast to non-digestible polymer particles (made of dietary fibers), which can only release nutraceuticals in the colon due to the activity of the colon bacteria, they may be released in the stomach or/and small intestine by digestible polymer particles formed of proteins.

When the encapsulated materials are digested, enzyme activity is vital in discharging nutraceuticals from the nanoparticles. In this regard, several researchers[72,73] investigated the release of beta-carotene from nanoparticles made of different proteins, including soy protein isolate (SPI), whey protein isolate (WPI), and sodium caseinate (SC), in simulated digestive juices made with and without hydrolytic enzymes. In the absence of proteases (pepsin and trypsin), the outcomes revealed that the dissolution rate of β-carotene in the simulated GI fluid was negligible for all prepared protein nanocarriers, whereas in the existence of proteases, the release rate varied depending on the carrier size, protein structure, and type of fluid. In comparison to SC nanoparticles (89.6 ± 3.0) and SPI nanoparticles (74.3 ± 6.6%), the dissolution frequency of β-carotene in WPI nanoparticles was indeed the lowest in the stomach fluid (5.6 ± 1.01%). The stable shape of the folded β-sheet pattern of β-lactoglobulin from WPI, which is less degraded by pepsin, was suggested as the cause of the low discharge rate from WPI nanoparticles. The discharge rate of β-carotene from WPI and SC nanoparticles was greater in the intestinal than in the gastric fluid, indicating that trypsin was more effective than pepsin. The existence of β-conglycinin in SPI, which is tolerant to trypsin action, was shown to be the cause of the low discharge frequency of SPI nanoparticles in the digestive juice. Additionally, the fact that SC nanoparticles were smaller (77.8 ± 0.2 nm) than SPI nanoparticles (371.8 ± 6.8 nm) contributed to their increased release rate in gastric juice and intestinal fluid. Complex matrices of polysaccharides and proteins are employed as encapsulating materials to alter the interfacial characteristics of nanoparticles.[74,75] Either the coacervation method, which involves combining polysaccharides and proteins with various electrical charges, or the layer-by-layer (LBL) technique, which entails successively adhering to the surface of nanoparticles a number of layers of polyelectrolytes with reverse electrical charges, are used to create them.[76]

The lipolysis rate of lipid nanoparticles can be affected by some factors, such as the type of surfactant used, the composition of the lipid matrix, the phase condition of the oil phase, the nutritional condition, and the particle size.[77] Surfactants reduce the interfacial tension between lipids and water, which is necessary for lipases to be absorbed onto the surface of lipid nanoparticles.[78] Effectively fixing surfactants, including Tween 80 and Poloxamer 188, impedes the attachment of lipases to the surface of the lipid nanoparticles. Conversely, ionic surfactants, especially cholic acid and sodium salt, facilitate the binding of lipases to the surfaces of the nanoparticles.[79] The size of the particles affects the rate at which the surface of the SLNs erodes. Reducing the size of the particles increases the available surface area for lipase attachment, perhaps leading to a higher degradation rate compared to bigger nanoparticles.[80] Regarding the lipid matrix of solid lipid nanoparticles, studies have shown that wax-based matrices exhibit lower degradation compared to glyceride-based matrices. Concurrently, the rate and extent to which the lipid matrix is digested might be affected by its physical condition.[81] Droplets of lipids are more prone to digestion than solid-state droplets. The fed or fasted state impacts the presence of biosurfactants and lipases in the gastrointestinal system. The degradation of lipid nanoparticles occurs more rapidly in the modeled fed-state medium than in the modeled fasted state medium, mostly due to the elevated amounts of lipases and biosurfactants present in the gastrointestinal milieu. Examining the rate at which lipid nanoparticles break down fat can be valuable in creating a more effective regulated-release method for

oral administration purposes.[82] Lipid nanoparticles that exhibit a gradual drug discharge pattern are advantageous for medications with low permeability, as the therapeutic agents can be absorbed while the nanoparticles degrade. Lipid nanoparticles that exhibit rapid drug release are more advantageous for enhancing the oral absorption of medicines with low water solubility.[83]

Nutraceuticals' Interactions with Other GIT Constituents

The chemical reactivity and molecular structure of nutraceuticals affect their bioavailability.[84] According to studies, biocompounds with molecular weights of more than 500 Da are less bioavailable.[85] Once within the GIT, the nutraceuticals may communicate with other GIT constituents that were either consumed with the food (surfactants, minerals, vitamins, proteins, carbohydrates, lipids, etc.) or were secreted by cells with specific GIT functions (mucin, bile salts, mineral acids and salts, phospholipids, hormones, enzymes, etc.). The bioavailability of nutraceuticals may be improved through some of these connections while other are decreased. For instance, the interaction between polyphenols and proteins produces a variety of outcomes. Proanthocyanidins and salivary proteins have been shown by some authors to interact, reducing the lubricating characteristics and changing the astringency.[86] According to some researchers, polyphenols may attach to proteins and alter their structure and function. The solubility of flavonoids and phenolic acids may vary as a result of binding to soy proteins, and the bioavailability of key amino acids (lysine and tryptophan) is reduced.[87] Similarly to this, phenolic substances may degrade due to pH changes in the GIT segments. For instance, according to Onoue, Ochi, and Yamada (2011), curcumin is unstable in an alkaline environment, while EGCG is unstable in both the neutral and acid environments of the small intestine.88 Some polyphenols (chlorogenic acid, caffeic acid, and catechin) may prevent the metallic ions in the GIT juices from acting pro-oxidatively.[89]

As previously demonstrated, the interaction between calcium ions and FFAs from lipid digestion, which is segregated as insoluble soaps, degrades the bioaccessibility of nutraceuticals. In this situation, ethylenediaminetetraacetic (EDTA) acid, as a chelation agent, is incorporated into foods to prevent these reactions.[90] The configuration isomerism of nutraceuticals may have an impact on their bioavailability in addition to their chemical reactivity.[91] Lycopene is a good example of this because, while being present in tomatoes in 95% all-trans form, it is only present in human plasma in 50% cis form due to isomerization in the GIT and greater absorption of cis-lycopene isomer than all-trans lycopene isomer.[92] According to some researchers who examined the bioavailability of hesperitin-7-glucoside, hesperidin was discovered in human plasma and urine in the form of the two enantiomers R/S with a mass ratio of 39:69. This finding suggests that the S-hesperidin enantiomer has greater efficacy than the R-hesperidin enantiomer.[93] The bioavailability of (−)-epicatechin and (+)-catechin, as well as the bioactivity of S-equol and R-equol and enantiomers, were shown to vary.[94]

Main Delivery Systems for the Encapsulation of Biocompounds Based on Nanostructured Lipid Carriers

According to the National Nanotechnology Initiative, nanotechnology is the investigation and application of structures with diameters ranging from 1 to 100 nm. Compared to microdelivery systems, nanodelivery systems provide a number of benefits. Some of the examples include improved solubility and bioavailability of bioactive constituents, protection of the contained substances from deterioration, sustained discharge, and long-term consistency of them.[95] Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are lipid nanoparticles with solid particle matrices (solid lipid-based nanocarriers).[96-98] The solid lipid or a mixture of solid lipids is substituted for the liquid lipid in oil-in-water (O/W) nanoemulsions, raising the melting temperature of the nanoparticle because highly structured crystalline systems have been created. SLNs were first developed at the beginning of the 1990s.[99] Due to the highly organized crystalline forms of solid lipids and bioactive substance ejection during storage, SLNs as nanocarriers exhibit various drawbacks, including an unexpected gelation propensity, polymorphic transition, and limited encapsulation effectiveness.[100] Because of the shortcomings of SLNs, Muller created NLCs, a new type of lipid carrier, in 1999/2000.[101,102] The next class of lipid carriers, known

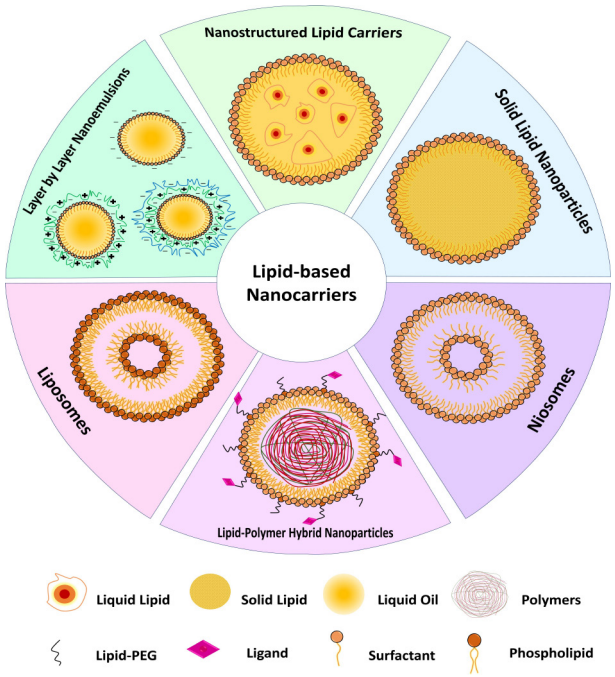

Figure 1. The main lipid-based nanocarriers.

as NLCs, utilizes both solid and liquid lipids. As a result of the production of more ordered solid matrices, this mixing lowers the melting point of the material. As a result, the loading capacity is increased, and the release is regulated[103] (Figure 1).

Benefits of nanostructured lipid carriers

As previously mentioned, NLCs reduce the number of issues with SLNs, including poor loading capacity brought on by the crystallization procedure and drug ejection during storage. Liquid oil alters the crystal structure of the NLC, resulting in bigger empty spaces that can lead to higher encapsulation efficiencies. This less-ordered structure also reduces the release of bioactive compounds throughout storage.[104] Some of the main NLCs advantages include; a) boosting bioactive compound solubility,[105] b) substantial delivery of substances,[106] c) biodegradable nature of the utilized lipids,[104] d) encapsulating both the hydrophilic and lipophilic biocompounds,[107] e) cost-effective compared to alternative delivery methods,[107] f) technology based on water and the removal of organic solvents,[108] g) regulated and prolonged discharge of bioactive compounds,[109] h) large-scale manufacturing due to the simplicity of preparation,[110] i) precise particle sizing, and j) more robust physical integrity.[111]

NLCs' components

Lipids

The primary component of lipid nanoparticles is lipid. In contrast to SLNs, a large portion of the solid lipid in NLCs is substituted by liquid lipid, resulting in a preferred ratio of 70:30 up to 99.9:0.1 for the two types of lipid.[112] The lipidic matrix has an impact on the colloidal, chemical, physical, and drug-release characteristics of NLCs. In light of this, the following variables should be taken into account while choosing an appropriate mixture of solid and liquid lipids (lipidic blend) for use in NLC formulation.[113] One of the most crucial factors affecting the loading efficiency of bioactive chemicals in the lipidic matrix is their solubility. A specified quantity of chemicals can be added to liquid lipids, stirred or sonicated, centrifuged or filtered (to remove non-soluble bioactive substances), and then the dissolved compounds can be quantified using chromatography or UV-Vis spectroscopy equipment.[114] Molecules of solid lipid and liquid lipid should mix well and be compatible with one another. As a result, neither the liquid lipid nor the lipid crystals dissolve in the oil phase, nor do they contribute to the solid lipid crystalline matrix. To avoid instability and phase separation at temperatures less than the lipid melting point, solid and liquid lipids should be dissolved in the quantities needed for the creation of NLCs.[113] The lipidic matrix needs to be resistant to chemical deterioration, such as lipolysis and oxidation. A food-grade lipid matrix is required. In other words, NLC preparation shouldn't leave behind any harmful residues. The lipids should have the ability to produce nanoscale particles. In other words, the liquid lipid's low viscosity and/or low interfacial tension cause the creation of extremely small particles.[113,115]

Liquid lipids

Oleic acid and medium-chain triglycerides (MCTs) are the two oils that are most frequently employed in the synthesis of NLC. The principal constituents of MCTs are the fatty acids caprylic (C8:0%; 50%–80%) and capric (C10:0%; 20%–50%). The fatty acid groups that make MCTs also include lauric acid, capric acid, caprylic acid, and caproic acid.[116] MCTs have a lower smoke point at ambient temperature, are liquid, have a smaller molecular weight than long-chain triglycerides (LCTs), and are rapidly metabolized for energy.[117] Additionally, MCTs (like Miglyol 812) digest more quickly than LCTs (like maize oil) and have stronger oxidation resistance (Table 2).[117]

These substances have no smell, but if they are hydrolyzed, the liberated fatty acids have a substantial impact on the scent of NLCs. The US Food and Drug Administration (FDA) has authorized MCTs as generally recognized as safe (GRAS) for continuous inclusion in a wide range of foods, including drinks, as a solvent, carrier, and emulsifier.[113] They are, however, regarded as suspenders and emulsifiers

Table 2. Comparison of the properties of long chain triglycerides (LCTs) and medium chain triglycerides (MCTs).

Type of triglyceride	Chemical characteristics Properties				Structure		Caloric Value (Calorie/gram)	Storage at adipose tissue
	Solubility	Smoke point	Hydrolysis rate	Presence of essential fatty acids	Type	Saturation status		
MCT	Water soluble	Lower smoke point	Fast hydrolysis	Negative	6-12 hydrocarbons	All saturated fatty acids	8.3	Less
LCT	Lipid soluble	Higher smoke point	Slow hydrolysis	Positive	13 to 21 hydrocarbons (long chain); ≥22 hydrocarbons (very long chain)	Both are saturated and unsaturated fatty acids	9.2	More

rather than solvers.[118] Many natural oils include oleic acid [cis-9-octadecenoic acid; C18:1(9)]. In the pharmaceutical and food sectors, it is employed as a surface-active agent and has no smell. Due to its oxidation susceptibility, it may produce free radicals that harm encapsulated bioactives. According to reports, oleic acid is an anti-inflammatory fatty acid that aids in the activation of certain immune-competent cell pathways.[119]

Solid lipids

The most popular solid lipids for NLC production are stearic acid, cetyl palmitate, glyceryl monostearate/monostearin, glyceryl palmitostearate, glyceryl behenate, bee wax, and cocoa butter.[120] Mono-, di-, and triacylglycerols of behenic acid (C22:0) make up glyceryl behenate, also known as Compritiol® 888 ATO, which possesses a significant melting point (~70 °C).[121] Because of the crystalline matrix's irregularities, it produces NLCs with a high encapsulation efficiency. A blend of mono-, di-, and triacylglycerols of stearic (C18:0) and palmitic (C16:0) fatty acids makes up glyceryl palmitostearate (Precirol® ATO 5). Its melted condition has reduced viscosity compared to Compritol® 888 ATO, which results in a regulated release of the medicine over time.[122] Precirol ATO5 reportedly created persistent lutein-loaded NLC colloids.[123] At least 72% of the monostearoyl glycerol in glyceryl monostearate is composed of mono- and diacylglycerol. It is safe and non-irritating to use glyceryl monostearate. As a result, it is frequently utilized as a stabilizer, emollient, plasticizer, and non-ionic emulsifier in cosmetics, foods, and medicinal formulations.[118]

Other forms of solid lipids, such as cetyl esters and cetyl alcohols (such as cetyl palmitate), are prohibited from being used in food. A biocompatible and food-grade substance, stearic acid (also known as octadecanoic acid), is a long-chain saturated fatty acid. It is one of the most prevalent long-chain fatty acids and may be found in both vegetable and animal fats. Stearic acid has a melting point of 69.6 °C. As a result, it is suitable for delivery.[124] Triglycerides like cacao butter can be utilized to make NLCs as solid lipids. It is made from cacao beans, and at least 40% of its fats are unsaturated. It has higher biocompatibility and lesser toxicity when compared to semisynthetic lipids.[116]

Emulsifier

By lowering the interface tension between both the lipid matrix and the aqueous solution during the formation of the particles, emulsifiers have been employed to stabilize lipid dispersions. Most of the studies employ the hydrophilic emulsifiers sodium deoxycholate, polyvinyl alcohol, polysorbates (Tween), and pluronic F68 (poloxamer 188). If necessary, emulsifiers that are amphiphilic (lecithin) or lipophilic (Span 80) are used in the manufacturing of NLCs. It has been discovered that using a combination of emulsifiers can help avoid aggregation more effectively. Tween 80 is an oleic acid and poly (ethoxylated) sorbitan-based non-ionic surfactant that is water-soluble. It is appropriate for stabilizing NLCs with a hydrophile-lipophile balance (HLB) level of 15 or above.116 The most important factor for the integrity of NLC nanoparticles when just non-ionic surfactants are used to stabilize the NLC complex is steric repulsion. Steric repulsion entirely insulates particles from the pH and electrolyte concentration. Tween 80 is less hazardous than ionic surfactants and is GRAS-approved for usage in certain food items.[125]

Natural sources, including soybeans, rapeseed, and eggs, can be used to extract lecithin, a hydrophobic and neutral surfactant. Lecithin's HLB number of 8 makes it unsuitable for NLC stabilization, although it can be employed in conjunction with other surfactants. All-trans-retinoic acid-loaded SLNs had smaller particles and a lower polydispersity index (PDI) after being treated with Tween 80 and egg phosphatidylcholine.[126] One of the two fatty acids in lecithin is removed to create lysolecithin, a kind of more hydrophilic lecithin. Lecithin is regarded as a GRAS component. In order to induce steric hindrance, Poloxamer 188 (Lutrol®F68; Pluronic® F68), a non-ionic surfactant with an HLB number of 29,118 encloses the nanoparticles in a dense film, which stabilizes NLCs.[127] Due to its low toxicities, it cannot be utilized as a direct ingredient in food items. Alcohol and sulfuric acid are esterified to produce sodium lauryl sulfate (SLS) or sodium dodecyl sulfate (SDS), a highly hydrophilic anionic surfactant (HLB ~ 40). By producing extremely potent electrostatic repulsion, it stabilizes NLCs. According to the USFDA, SDS is regarded as a GRAS component for use in food (21 CFR 172.822).[128]

Encapsulation of bioactive substances in NLCs

The nanoparticles' various locations can accommodate bioactives. Three models of incorporating bioactives inside NLCs include homogenous matrices of solid solution and bioactive compound-enriched shell/core (Figure 2).

Homogenous matrices of solid solution

In this paradigm, the bioactive substance is uniformly and molecularly distributed across the lipid matrix, and the bioactives are released by a diffusion mechanism. When no surfactant or bioactive-solubilizing surfactant is utilized in cold-HPH, this paradigm manifests.[129]

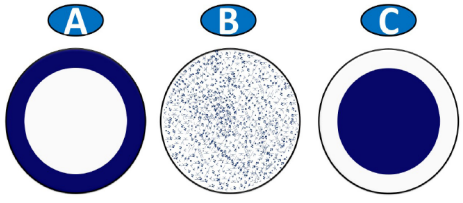

Figure 2. Nanostructured lipid carriers and the main incorporation models of bioactive compounds. Bioactive compound-enriched shell (A), homogeneous matrix (B), and bioactive compound-enriched core (C).

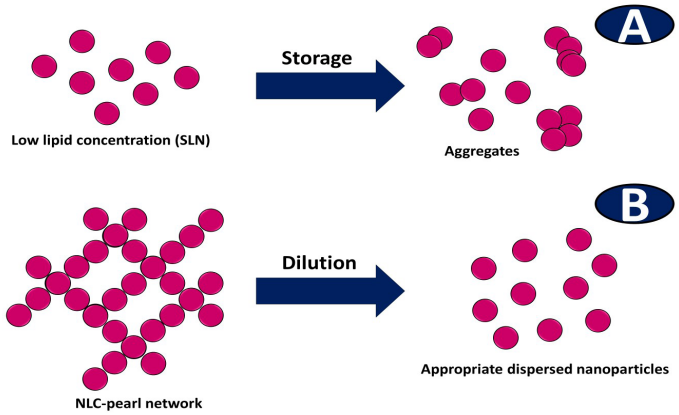

Figure 3. The behavior of low- and highly-concentrated nanostructured lipid carrier dispersions upon storage. In low lipid concentration dispersions (solid lipid carrier), the particles can collide which results in aggregation (A), and pearl-like network formation occurs in highly concentrated nanostructured lipid carrier dispersions with a stabilizing effect upon storage (B).

Bioactive compound-enriched shell

This paradigm happens in Hot-HPH when the bioactive ingredient divides from the lipid part to the water part at a higher temperature, and afterward, it re-partitions to the lipid part during the cooling stage, resulting in a concentration of the bioactive ingredient on the lipid nanoparticles' shell. As the bioactive component is more soluble in the aqueous phase, when the temperature rises, the partitioning rate also rises. Due to the solubilization and precipitation mechanisms in this instance, the bioactive molecule is released in bursts.[130]

Bioactive compound-enriched core

In this scenario, the bioactive substance dissolves in the lipid and melts at or near its saturation solubility, which causes the medicine to precipitate before the lipid crystallizes again. The lipid around the bioactive substance core is recrystallized with further cooling. In this instance, the persistent release is seen as a result of the bioactive compound's saturation solubility in the lipid.[116]

Stability of NLCs

Liposomes, nanoemulsions, mixed micelles, and other colloidal structures may also be present in NLCs, which might affect the stability of the formulation. Collisions may lead to aggregation and perikinetic flocculation during long-term storage. Zeta potential (ZP), thermal analysis (Differential scanning calorimetry, DSC), and measurements of particle size (Photon correlation spectroscopy, PCS, Laser diffraction, LD) are typically used to examine the physical stability.[131] A pearl-like effect (Figure 3) maintaining the lipid nanoparticle distribution versus aggregation is seen in extremely concentrated NLC dispersions caused by network development. This network is disrupted after dilution with blood or digestive fluids, generating single, non-aggregated particles.[132] The particles are fixed in the pearl-like network, diffusion is decreased, and aggregation is thereby avoided. Two methods may be used to guarantee the NLCs' physical stability in terms of gelling or aggregation during storage: 1) freeze-drying the dispersion to get rid of the water; 2) putting stabilizers in the emulsion. A freeze-dried formula should not only keep a suitable look and be simple to reconstitute in water with a brief reconstitution time, but it should also preserve the functionality of the encapsulated bioactive component and not cause any modifications in the nanoparticles' particle diameter. Aggregation, however, has been noted in freeze-dried formulations devoid of cryoprotectants.[133] To maintain NLCs' physical stability, preservers are employed. Preservatives, however, can potentially make NLC unstable. After 3, 6, and 12 months of storage at room temperature, the impact of eleven preservatives on the zeta potential, size, and physical stability of a Q10-loaded NLC dispersion was examined. It was discovered that seven of the eleven preservative elements investigated may be used to sustain NLC colloids, with Hydrolite 5 being the better decision for Q10-loaded NLCs. Using preservatives for NLC storage is preferable to the freeze-drying approach.[134]

NLC applications in foods

NLCs are one of the useful delivery methods used in the food, cosmetics, and pharmaceutical sectors. The connection between dietary habits and overall health is a topic on which people are increasingly careful these days. Functional foods are those that offer additional health advantages over and beyond their fundamental nutritional benefits. However, cutting back on fatty meals may result in dietary deficits of nutrients that are fat-soluble, including certain flavonoids, phytosterols, essential fatty acids, carotenoids, vitamins, and other lipophilic minerals. Therefore, it is necessary to include these functional ingredients in diets.[135,136] However, there are several drawbacks to bioactive substances, such as their vulnerability to environmental stressors including oxygen, light, pH, and others; their limited absorption via intestinal cells as a result of their lipophilic character; and their poor constancy during the course of manufacturing and storage. Consequently, utilizing nanodelivery systems like NLCs may be able to both safeguard bioactives from

harmful elements and maximize their release, absorption, penetration, and eventually bioavailability.[137] Since it is a lipophilic essential vitamin and is susceptible to oxidation, vitamin D3 cannot be added to aqueous-based formulations. These factors make encapsulation a beneficial process for increasing their ability to disperse in aqueous conditions. Poor water solubility, chemical instability, low bioavailability, and susceptibility to oxidation characterize carotenoids as nutraceutical substances.

Carotenoids must thus be included in an appropriate nanodelivery method. Omega-3 fatty acids are prone to oxidative degradation, which makes fortified foods smell bad. It has been demonstrated that encapsulating omega-3 fatty acids can shield them from oxidative destruction and, as a result, can cover up their unfavorable scents. The important plant sterols, known as phytosterols, have an extremely high melting range, are insoluble in water, and are highly prone to oxidation. Encapsulation methods can avoid this oxidation. A significant class of natural polyphenols known as flavonoids has poor bioavailability and an unpleasant taste.[116,138] These factors make integration into a suitable nanodelivery system beneficial. Numerous investigations have been conducted up to this point about the encapsulation of biocompounds within NLCs. More details on the use of NLCs in food are provided in Table 3.

Oral Delivery Systems and Their Biological Fate

A bioactive chemical must exist in an aqueous solution, which is a necessary condition for practically all processes of absorption. This information is based on the substance's water solubility and rate of dissolution. Due to their larger surface area, lipid-based nanoparticles (LN) provide improved bioavailability. Additionally, they boost the level of elements in the systemic circulation through lymphatic and systemic transport. Since hydrophobic and insoluble bioactive chemicals cannot dissolve in water, LN is regarded as a promising and secure nanocarrier for their administration in aqueous environments. Improving the emulsion integrity of these nanoparticles under many difficult circumstances, such as those of food preparation (drying, high pressure, heating, etc.) and the gastrointestinal milieu (digestive enzymes, bile salt, and low pH), investigating communications between bioactive substances and nanoparticles for effective encapsulation,

Table 3. Some of the main bioactive compounds incorporated into NLCs formulations.

Incorporated bioactive compounds	Study outcomes	Ref.
Coenzyme Q10	The average encapsulation efficiency of developed NLC was about 98.4 ± 0.3%. In 3 months' storage, the particle size was 190 ± 30 nm with polydispersity index lower than 0.1. Hence, it demonstrated a promising perspective for daily consuming and industrial production	139
Krill oil	The results demonstrated the small size (96%) of the developed NLC. Appropriate physicochemical stability was revealed by long-term storage at different temperatures and it had protective effect on bioactives in krill oil against photo oxidation	140
Quercetin and linseed oil	The quercetin and linseed oil co-loaded NLC was stable for more than 3 months at 25 °C. Hence, NLC could be a promising vehicle for delivery of lipophilic bioactive compounds and ω-3 unsaturated fatty acids in food industry	141
Cinnamon essential oil	The average size and the encapsulation efficiency of the developed NLC were in the range of 100–120 nm and more than 82.1 ± 0.03%, respectively. It is concluded that this delivery system might be useful for the fortification of beverages	142
Cardamom essential oil	The developed NLC had acceptable size (90%). The results showed that the developed NLC could be used as food supplements	143
Turmeric extract	Turmeric extract loaded NLC with an average size of 112.4 nm showed significant physical stability and a sustained release pattern. The results indicated that produced NLC could be used in food products with high functional effects	144
Astaxanthin	The average encapsulation efficiency of the developed NLC was about 94.8 ± 1.0%. Antioxidant study showed that astaxanthin could be encapsulated in NLC without loss of antioxidant activity	145
β-carotene	The smallest particle size was observed in the formulation containing 2% poloxamer 407 and solid lipid/liquid oil ratio of 10:1. The encapsulation efficiency of optimal sample was 97.7% and remained stable for 14 days at 25 °C	146
Vitamin A Palmitate	The poloxamer concentration increment up to 6% resulted in a decrease in particle size and particle size distribution with encapsulation efficiency of 98.5% and it was stable during the storage at 25 °C for two months	147

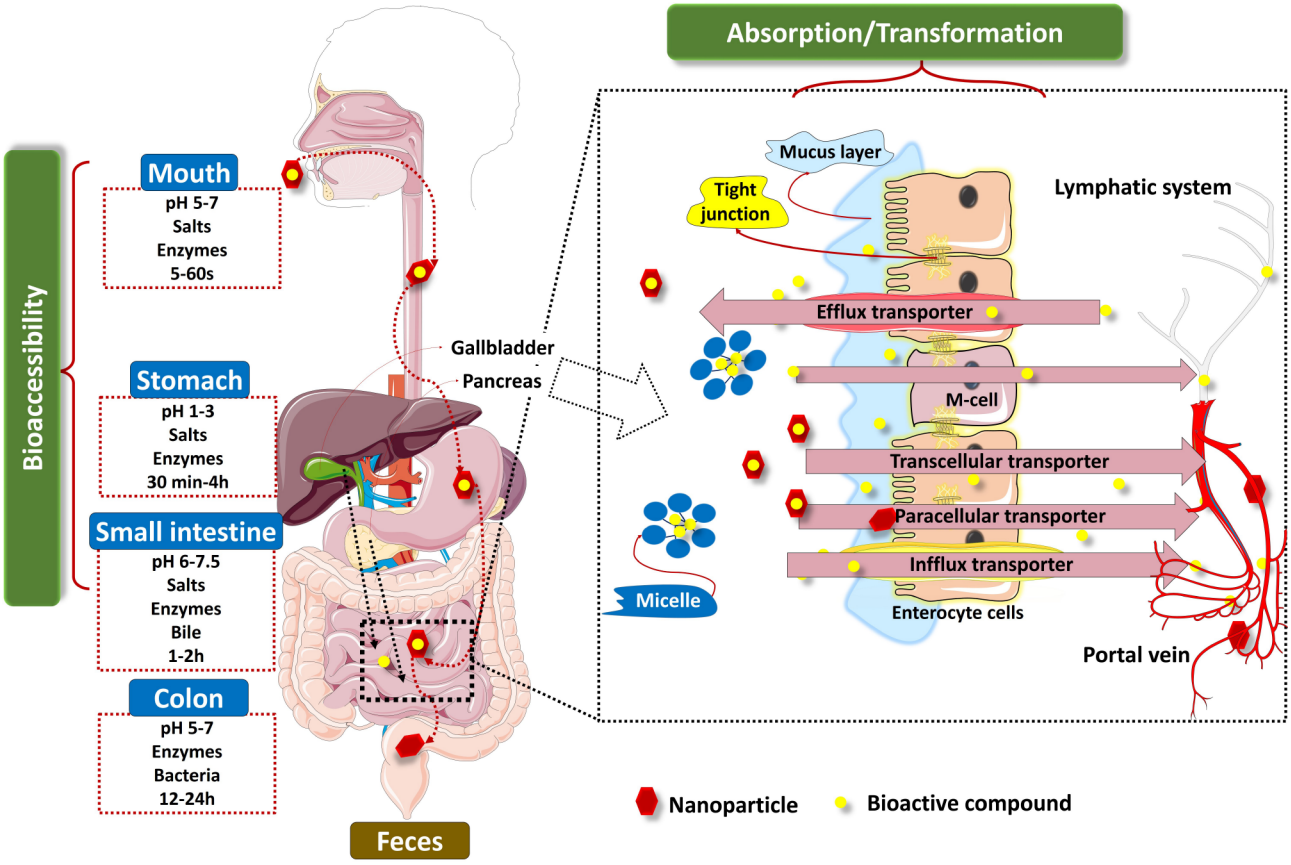

Figure 4. The schematic of the biological fate of nanocarriers loaded with bioactive compounds. Liberation, solubilization, interactions (bioaccessibility), mucus layer, tight junction transport, Infflux (active) transporters, efflux transporters (absorption), as well as chemical degradation, and metabolism (transformation) are the key elements limiting the oral bioavailability of bioactive compounds.

and understanding the biological fate of these particles after oral regime have all been demanding tasks for LNs. The two more gradual rate-determining procedures that surround oral nutrient absorption are the frequency of dissolution and the pace of nutrients penetrating the biomembrane[148] (Figure 4).

The most significant impact of particle size diminution, however, is shown in the improvement in the dissolving rate through augmentation of the particle surface area since intrinsic solubility is practically unaltered.[149] Additionally, reducing the particle size reduces the thickness of the diffusion layer, which speeds up the dissolving process by allowing molecules to be solvated to enter bulk solution more quickly.[150] The biological fate of LN taken orally has received very little research, and it is still unknown how LN enters the bloodstream through the intestinal lumen. In their research on the creation of SLN and NLC, Wang and colleagues[151] employed several natural polymeric coating ingredients (carrageenan and pectin), and the resulting nanolipid dispersion carriers were then transformed into solid powders using the nanospray drying method. The SLN powder was aggregated and had an uneven shape after being spray-dried, while NLC formulations had tiny, homogenous, well-separated spheres of powder. The ideal NLC formulation had 20–30% oleic acid and either pectin or carrageenan as the coating substance. Therefore, if the formulation of the lipid delivery system is properly targeted, nano spray drying technology has the capacity to generate spherical, homogeneous, and sub-microscale lipid powder particles. Because of their numerous beneficial structural and physicochemical characteristics, complex or hybrid nanoparticles comprised of two or more biomaterials have attracted growing interest in recent years.[152]

Consequently, the initial physicochemical features of ingested LN, including the particle diameter, surface qualities, composition, and structure, dictate their biological destiny in the gastrointestinal system, and their absorption mostly takes place in the small intestine. LN can be digestible or indigestible according to its composition, and each form of LN has two unique physiologic consequences. According to Wang and Luo's research, each form of LN has specific absorption processes and uptake routes at the molecular, cellular, and entire body levels.[153] While the in vitro model of Caco-2 cell lines enables the investigation of particular mechanisms of LN transcytosis in cells, and integral nanoparticles were observed on the bottom side of these cell monolayers in certain research, there is still debate regarding whether integral LN can be absorbed and transported throughout the intestinal epithelium. In vitro models are unable to completely replicate key features of human intestinal physiology, like the structure of the intestinal villi. Additionally,

these simulations are unable to offer comprehensive and ongoing data on the absorption and digestion of LN. As a result, investigators have tried to study the transportation of integral LN throughout the epithelium of the intestine using in vivo models. Nevertheless, developing a suitable in vivo model is challenging due to the intricate nature of the human body's physiological processes and the small size of LN, which makes identification very challenging. Yuan and colleagues synthesized ODA-FITC and utilized it as a fluorescent probe to mark stearic acid SLN produced using the solvent diffusion technique.[120] The researchers discovered that the oral administration of integrated SLN resulted in a transport efficiency of approximately thirty percent. Furthermore, a significant majority of the SLN (around 77.9%) was carried into the systemic circulation through the lymphatic system. Nevertheless, the fluorescence probe employed in this investigation retains the ability to generate fluorescence even after dissociating from nanoparticles. Consequently, it is not appropriate to rely on the fluorescence signal as a reliable indicator of intact nanoparticles. Subsequently, Chen and colleagues created a combination of lipids forming a protective outer layer and an inner core comprising micelles loaded with FITC-E4. They then marked the outer lipid layer with rhodamine phospholipid.[121] Basically, they used distinct fluorescence probes to mark both the enclosed cargo and the lipid shell individually. The fluorescence microscope images indicated that FITCE4 could penetrate deep into the villi or even the capillaries. However, the majority of the solid lipid shell of the NPs continued in the epithelial cells, suggesting that the integral nanoparticles were not able to be absorbed by the intestinal epithelia. In an additional investigation, Hu and colleagues established a new near-infrared fluorescent probe (P2) that responds to changes in its environment. When P2 comes into contact with water, its fluorescence is suppressed. This probe was used to track the fate of SLN in living organisms.[122] The rationale behind this detection method is that the fluorescence signal is diminished when the probes discharge from the hydrophobic lipid core into the hydrophilic external setting. The outcomes of the research showed that the likelihood of intact SLN absorption via oral delivery is minimal. This conclusion was drawn from the absence of fluorescence signals in different tissues and organs (brain, blood, kidney, lung, spleen, liver, etc.), except for the gastrointestinal tract. Nevertheless, in a subsequent investigation carried out by the same team, they disputed prior findings by increasing the overall dosage of SLN, as well as the total dosage of fluorescence, and discovered that signals from fluorescence could be traced in the bloodstream, lymphatic system, and liver.[123] While SLN can be delivered by M cells as intact nanoparticles into the bloodstream and ultimately reach the liver, only a minimal quantity of SLN can pass through this pathway. The majority of the SLN underwent degradation and then discharged the encapsulated cargos when entering the gastrointestinal tract. The cargos that have been released will either be absorbed via passive diffusion or become part of mixed micelles for subsequent absorption. Nevertheless, the durability and coherence of Tween 80 dispersed SLN in both of the aforementioned tests cannot be assured throughout transportation in the gastrointestinal tract. Therefore, only a minimal quantity of essential SLN was present upon entering the epithelia of the intestine for uptake. Practical verification is still needed to determine whether indigestible LN may be absorbed and transported through the epithelium of the intestine in the form of integrated nanoparticles.

Encapsulating Technological Barriers, Food Safety Concerns, and Regulatory Issues

Micro and nano-encapsulation technological challenges

Even though only a few methods, such as spray or freeze drying, are widely used in the pharmaceutical and food sectors, a wide range of strategies have been documented in the recent past for encapsulating bioactive substances. Recent reports of innovative, developing, or enhanced traditional procedures should be further investigated for industrial applications in light of their maximum throughput, good product quality, affordable manufacturing costs, minimal handling difficulties, and safety considerations. Every technique has drawbacks and particularities that make it more difficult to use, but these drawbacks should be taken into account for more research in order to help move the technique from the lab to the pilot size and eventually the industrial level. Therefore, a number of suggestions for the complicated challenges in micro- and nanoencapsulation might be as follows: a) discover the ideal GRAS polymers for each encapsulation method and assess each one's comparative effectiveness; b) investigate the ideal processing circumstances, including technical setups and formulations, to improve encapsulation effectiveness, product stability, and target discharge profile even further; c) the best encapsulation method for any particular bioactive component may be determined by a comparison of the various encapsulation procedures; d) instead of employing different organic solvents that are unsafe for ingesting (such as those used in antisolvent precipitation), look into alternatives; e) to boost throughput, lower energy consumption, and promote operational efficiencies, the mechanical design should be improved; f) find unique nanoparticles and emerging technologies that have particular uses in biological and food processes; g) create a multi-compartment system to accommodate several deliveries of various bioactive substances; and h) examine the toxicity implications and the synergistic effects of numerous distribution methods or co-delivery in biological and food systems.[154]

Safety aspects

In the food and pharmaceutical industries, the use of nanotechnology for nutrition or medication encapsulation has grown in favor. In addition to the many advantages of nanoencapsulation, it has recently generated a variety of safety, ethical, and regulatory concerns regarding the

effects of nano-sized transporters on host health and the environment. As a result of the possible toxicity or harm that nanoparticles pose to human health and the environment, public opinion is shifting.[126] However, there is still a need for further risk analysis and knowledge on the safety of nanoencapsulation, especially in regard to long-term toxicity.

Nanocarriers are special because of their extremely tiny size, which enables them to penetrate various biological barriers such as firmly bonded intestinal epithelial cells via the transcellular or paracellular pathway through enterocytes, respectively, and enter tissues. As a result, they can readily participate in the majority of biological processes that could result in toxicity. The aggregation of nanoparticles in the enterocytes can have negative consequences, such as inflammatory bowel disease, because the small intestine has a high absorption rate for nanoparticles.[155] According to certain animal experiments, when nanoparticles are accumulated in one organ, such as the lung or stomach, they can enter the bloodstream and travel to other tissues, where they might trigger inflammatory reactions.[156] Laceration and acute inflammation may also result from the absorption of nanoparticles with larger concentrations and more reactive surfaces per unit mass, as well as those with particular chemistry and functionality, according to studies. Additionally, due to their large surface area and increased reactivity, food nanoparticles found in the intraepithelial space might compete with regular food in terms of absorption.[157]

Various chemical polymers are used throughout the encapsulating process to create nanoparticles that may be hazardous. In this situation, natural biopolymers could be the first option for drug delivery methods since they are GRAS substances, biodegradable, and safe for host consumption. The vitality of cells can, however, also be adversely impacted by natural biopolymers. The flavonoid quercetin was enclosed in chitosan-coated nanoliposomes, according to a study by Hao and colleagues (2017).[158] At a dosage of 10 mg/mL in HepG2 cells, the MTT experiment revealed that the encapsulated quercetin had significantly lower cell viability (40.92%) than natural quercetin (46.67%). On the contrary, oral administration of aspirin, curcumin, and free sulforaphane in conjunction with chitosan-solid lipid nanoparticles did not cause any harm in acute, subacute, or subchronic trials in BalB/c mice.[159] Guar gum succinate has also been mentioned as a medication delivery method for the colon that doesn't negatively impact C3H10T1/2 cell proliferation.[160]

The cytotoxicity of a nanoparticle can be influenced by its surface characteristics. The harmful effects of untreated nanoparticles can be lessened by covering them. Gupta and Wells (2004) investigated the cytotoxicity characteristics of magnetic nanoparticles when exposed to human fibroblasts and assessed the results using the MTT test. They found that PEG-coated superparamagnetic iron oxide nanoparticles were more cell-viable than uncoated particles. The toxicity of a particle can also be impacted by its surface charge. According to studies, negatively or neutrally charged nanoparticles are less harmful than positively charged ones.[161] As a result, various coatings or functionalization units on the surface of nanoparticles may vary the surface chemistry, which in turn can impact the survival of cells in humans and other biological systems.[162] Cruz, Garca-Estrada, Olabarrieta, and Rainieri (2015) proposed that two aspects may be taken into account when assessing the toxicity of nanoparticles: a) the existence of polymers employed in the final formulation, and (ii) the impacts and alteration of the nanoparticles in the GIT system.[163]

Regulatory aspects

There is no specific law that is implemented internationally that regulates the use of nanoparticles in the pharmaceutical and food industries. However, the majority of nations lack clear laws governing the evaluation of encapsulated nanoproducts' risks. Even inconsistent information flow between nations is reportedly dangerous for the environment and human health, and it may also prevent the global sale of innovative beneficial items.[154] Most likely, only the European Union (EU) has a precise legislative definition of nanomaterials, whereas laws in other nations merely have an implicit definition that serves as a basic industry guideline. The European Commission (EC) defined a nanomaterial (regulation no. 1169/2011–"Engineered nanomaterial") as "any intentionally produced material that has one or more dimensions of the order of 100 nm or less, or that is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions in the order of 100 nm or less". This definition includes structures, agglomerates, or aggregates, which may have a size above the 100 nm threshold.[154,164] Regulation (EU) no. 10/2011 on materials for food contact and risk assessment states that nanoparticles may result in varied toxicological characteristics and should thus be assessed on a particular circumstance basis. Only those nanoparticles that are specifically permitted or listed in Annex I of Regulation (EU) No. 10/2011 may be employed. The functional barrier idea, which allows for the movement of some prohibited components contained in multi-layer materials, should not be applied to nanoparticles. On intelligent and active materials, risk assessment of particles by particular circumstance research is equally valid.[164]

Although the FDA produced draft advice for the industry on the safety concerns of innovative food industry technologies, it does not have a delicate concept related to nanoparticles within the food and pharmaceutical industries.[165] According to the guidelines, nanomaterials are defined as elements or commodities that fall within the nanoscale range in at least one dimension (between 1 and 100 nm), as well as agents or products that exhibit chemical, physical, and biological properties linked to nanomaterials despite not being nanoscale in size. Additionally, the guidance outlined some obligations for the industry; a) to keep track of modifications made to food materials, such

as physicochemical characteristics and impurities; b) to assess the safety of foods following their modifications; c) to submit a regulatory evaluation to the US FDA; and d) to identify a regulatory concern for consuming of the novel food commodity. The FDA in the USA asserts that the laws in place are sufficient for assessing the safety of nanomaterials. The regulatory bodies of other nations also have regulations, and they advise that before going on sale, food goods treated with nanomaterials should undergo safety testing.[126]

Conclusion

The primary goal of food scientists and producers is the creation and production of functional foods with novel properties that promote customers' health. Food enrichment with natural biocomponents derived from animal and plant sources is being given considerable attention. Unfortunately, a lot of these biocomponents have poor water solubilities, are hydrophobic, and are challenging to incorporate into food systems. Additionally, several biocomponents possess a very poor bioavailability (<5%), including carotenoids, phytosterols, polyphenols, and others. As a result, current research has concentrated on creating fresh methods for enhancing the health and nutritional profiles of functional foods while lessening their environmental effects. In this regard, researchers now have access to cutting-edge nanomaterials thanks to nanotechnologies that can help improve the bioefficiency, security, and safety of food.

The bioavailability of bioactive constituents employed in food functionalization is a crucial component of food bioefficiency. Several investigative teams have examined the bioavailability of bioactive compounds in organic food systems such as seed cereals, vegetables, etc., while others have examined the bioavailability properties of concentrated matrices, like dietary supplements. Still, other research teams have looked at the impact of various kinds of bioactive-loaded nanosystems on oral bioavailability. According to the findings of these investigations, bioavailability is a complex process of biological and physicochemical mechanisms that affects how biomolecules are distributed inside our bodies to maximize their therapeutic impact. In this regard, to promote the bioavailability of bioactive compounds, the encapsulation technique has been considered a novel and effective strategy for both in vitro and in vivo circumstances. In terms of greater protection, higher stability, prolonged discharge profile, and enhanced bioavailability of bioactive chemicals, nano-encapsulation performs better than micro-encapsulation. The choice of carrier materials, their physicochemical and rheological qualities to enable the preservation of the target bioactive ingredient, and appropriate encapsulation processes are ultimately what determine the effectiveness of the utilization of micro- and nano-encapsulation. Recently, there has been growing interest in lipid-based transporters, particularly lipid nanoparticles (such as SLN and NLC), as novel nano-encapsulate systems. As opposed to other lipid-based nano-systems such as polymeric micelles, nanoliposomes, and nano-emulsions, they are at the forefront of practical utilization, exposing remarkable performance in nanoencapsulation functions.

Future research will be necessary to overcome the constraints of micro- and nano-encapsulation procedures, enhance the already-used techniques, formulations, and encapsulate systems, and satisfy market expectations for their industrial-scale manufacturing. In order to investigate the impact of bioactive-loaded micro- and nano-capsules on cell viability as well as the adsorption, distribution, metabolism, and excretion (ADME) profiles in humans and other biological systems, research focused on their use in food and biomedical applications should also be prioritized. Additionally, it's important to continue researching the accumulation of nanoparticles in organs and tissues and to assess the potential toxicity of these accumulations. Finally, it is necessary to standardize the techniques of evaluating the pharmacokinetic properties, the nutritional impact, the risk of poisoning, and the influence on the environment in order to prevent the discrepancy between the data obtained by various studies.

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Conflict of Interest

There was no conflict of interest.

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