Recent developments in encapsulation of α-lipoic acid for enhanced bioavailability and stability

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Abstract

α-lipoic acid (LA) is a potent antioxidant available in various plant and animal sources. Of late, there is high market demand for LA-based nutraceuticals, owing to enhanced occurrences of oxidative stress-based diseases. However, the effectiveness of LA is challenged with its low solubility, less stability, and low bioavailability. In addition, the unpleasant taste of LA limits its applications in food systems. In this context, encapsulation techniques can modify the chemical and biological properties of LA and improve its solubility and stability in the aqueous medium, which in turn helps in the development of different innovative therapeutic products based on LA. Different encapsulation techniques such as inclusion complexes, spray drying, electrospraying, solid lipid nanoparticles (SLN), emulsification, and liposomes have been explored for the encapsulation of LA. This review focuses on the biological activities of LA in terms of antioxidant, antidiabetic, anticancer, and anti-inflammatory properties, and the scope of encapsulation to enhance these properties, as evidenced through *in vitro* and *in vivo* studies. Furthermore, this article will help researchers and industrialists to select the suitable encapsulation method based on their requirement for delivering LA to achieve its optimal therapeutic potential.

Keywords: bioavailability, biological properties, delivery system, encapsulation, lipoic acid, stability

Introduction

α-lipoic acid (LA), chemically known as 1,2-dithiolane-3-pentanoic acid, has emerged lately as an important bioactive compound for dietary supplements. This bioactive compound is widely used to metabolize carbohydrates efficiently for proper functioning of different body organs. LA is well-recognized for its therapeutic potentials like scavenging of free radicals (antioxidant activity), anti-diabetic potency, remedial action in peripheral neuropathy, excellence for skincare, and as an vital geriatric supplement (by restoring depleting glutathione levels) (Shay *et al*., 2009). Market size of LA in 2020 was USD 805.7 million, which is expected to expand at a Compound Annual Growth Rate (CAGR) of 6.3% from 2021 to 2027. Being a valuable supplemental biomolecule, its pre-delivery sustenance, bioavailability, and site-specific delivery in the body are important aspects.

The common dietary sources of LA are yams, spinach, broccoli, yeast, potatoes, tomatoes, beets, Brussels sprouts, carrots, and meat, especially from portions such as muscles' meat, heart, kidney, and liver (Bilska-Wilkosz *et al*., 2017) (Table 1). The content of LA is higher in meat compared to fruits, vegetables, and grains. Lipoyllysine, a derivative of LA, is usually estimated to determine the content of LA in plant and animal tissues. Reportedly, spinach contains highest amount (3.15 mg/g of dry

weight) of lipoyllysine compared to other plant sources (0.4–1.0 mg/g of dry weight) (Xiao *et al*., 2018); interestingly, for animal sources, it is reported that darker part of meat contains higher amount of LA compared to light color meat (Mattulat *et al*., 1992).

However, dietary sources are not sufficient to meet our daily requirement of LA, and thus consumption of LA supplement (50 to 600 mg/day) with high bioavailability is recommended. On the other hand, the sensitivity of LA towards the environmental factors, such as light and temperature, creates a great challenge for maintaining the stability of the compound. Furthermore, its targeted delivery to the small intestine, in case of oral route of delivery, is another major challenge. Encapsulation of LA is a useful and feasible solution in this regard that would not only protect the bioactive but could also aid in its site-specific sustained release (Dutta and Bhattacharjee, 2017).

Several authors have reviewed the therapeutic properties of LA and its efficacy against different diseases, its mechanism of action, and bioavailability (Table 2); however, a review on the different techniques used for encapsulation of LA, and properties of the encapsulates is still unavailable. This current review focuses on several therapeutic potentials of LA along with the importance of different techniques used for encapsulation of LA, describing the effectiveness of individual technique to deliver LA with enhanced stability and bioavailability. Thus, the review will provide direction for future studies in the area of encapsulation of LA, and their applications for the development of therapeutic products.

Chemical and Functional Properties of LA

The therapeutic potential of LA is well-known for decades. LA plays an important role in mitochondrial energy metabolism while acting as an essential cofactor for mitochondrial α-ketoacid dehydrogenases (Solmonson *et al*., 2018). Interestingly, LA gets absorbed in intact condition as consumed from various dietary sources and gets accumulated in different tissues. Reportedly, orally administered LA may not be utilized as a metabolic cofactor but shows distinctive biochemical activities with vital pharmacotherapeutic role against physiological injury from host (Soczynska *et al*., 2008). It acts as a potential biological antioxidant, detoxifying agent, and antidiabetic drug. Furthermore, LA plays an important role in preventing age-related disorders, such as cardiovascular disorders, and cognitive and neuromuscular deficiencies (Smith *et al*., 2004). Also, LA is proved to inhibit acrylamide-induced neurotoxicity in SH-SY5Y neuronal cells (Song *et al*., 2017). All these therapeutic potentials of LA at the molecular and cellular levels have attracted a lot of interest from the scientific community as well as from the consumers to use it in pharmacotherapy, and also as a nutritional supplement (Shay *et al*., 2009).

Mechanism of action of LA as therapeutic compound

Despite less and temporary accumulation of LA in the cells, it has shown therapeutic potential when administered orally. Several researches on the therapeutic effects of LA have been reported, ranging from antioxidants to metal chelators to cell signaling pathway modulators (Figure 1), which have been discussed below.

LA as antioxidant

The chemical activity of LA is primarily due to the presence of dithiolane ring. Both the reduced (dihydrolipoic acid, DHLA) and oxidized forms (LA) act as potential redox couple with standard reduction potential of −0.32 V that results in their antioxidant potency (Tibullo *et al*., 2017). It was reported that LA and DHLA are able

Table 1. Different sources of α-lipoic acid.

Source of α-lipoic acid	Place of availability and content (µg/g)	Form of lipoic acid (LA)	References
Spinach	Leaves (3.15)	Lipoyllysine (LA covalently bound to lysine)	Halliwell and Foyer, 1978
Potato	Tuber (3.09)	LA	Saha *et al*., 2018)
Tomatoes	Fruits (0.56)	LA and dihydrolipoic acid (DHLA)	Incerti *et al*., 2009
Broccoli	Flower (0.94)	Lipoyllysine	Lodge and Packer, 1999
Brussels sprouts	Mitochondria/chloroplasts (0.39)	Lipoyllysine	Lodge and Packer, 1999
Green pea	Fruits (0.39)	Lipoyllysine	Lodge and Packer, 1999
Beet & carrot	Root (not reported)	LA	Griffin, 2020
Animal tissue	Kidney (2.64), heart (1.51), liver (0.86), skeletal muscle (0.97)	Lipoyllysine	Lodge and Packer, 1999

Table 2. Selected previously published review papers on lipoic acid (LA).

Review objective	Major sections of the review	References
Antioxidant and pro-oxidant activities of LA and dihydrolipoic acid (DHLA)	• Free radical scavenging properties of LA and DHLA • Strong reductant property of LA and DHLA as redox couple • *In vitro* pro-oxidant activity of LA and DHLA	(Moini *et al*., 2002)
LA for the treatment of cardiovascular diseases	• Mechanism of LA for the treatment of cardiovascular diseases • Blood lipid modulating and hypertension modulating characteristics of LA and its role in preventing cardiovascular disease	(Wollin and Jones, 2003)
Potential of LA as "drug of the future"	• Therapeutic properties of LA against different diseases related to oxidative stress • Requirement of detailed study on the involvement of LA in cell growth and differentiation	(Bilska and Włodek, 2005)
LA as a novel treatment for Alzheimer's disease (AD) and related dementias	• Properties of LA were explored with particular emphasis on how this agent, particularly the R-α-enantiomer, is effective to treat AD and related dementias. • Role of LA in maintaining the level of pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase (KGDH)	(Holmquist *et al*., 2007)
Therapeutic properties and possible utilities of LA in disease treatment	• Bioavailability and safety of oral LA supplementation • Antioxidant property of LA and DHLA • Different therapeutic activities of LA	(Gorąca *et al*., 2011)
LA with antioxidant effects in biological systems	• Antioxidant activity of LA through quenching ROS as well as chelation of transition metal • Chemistry and metabolism of LA • Discussions on the effects of LA and DHLA on diabetes and cardiovascular diseases	(Rochette *et al*., 2013)
Therapeutic applications of LA	• Therapeutic potential of LA reported in research article in open patents • Impact of conjugation of LA with other bioactive compounds in treatment of various diseases • Various methods for stabilizing LA formulation for improved therapeutic potential	(Koufaki, 2014)
LA as potential antioxidant and anti-inflammatory agent	• Molecular pathway for the antioxidant and anti-inflammatory properties of LA • Impact of LA consumption on reducing glucose level for diabetic patients	(Tibullo *et al*., 2017)
LA for the treatment of diabetic peripheral neuropathy	• Role of LA for the treatment of diabetic peripheral neuropathy • Impact of LA consumption on nerve conduction velocities in patients with diabetic peripheral neuropathy at placebo-controlled trials	(Han *et al*., 2012; Namazi *et al*., 2018)
LA as anti-inflammatory agent	• A systematic review and meta-analysis of clinical trials • Impact of LA consumption on serum inflammatory mediators' concentration such as tumor necrosis factor-alpha (TNF-α), c-reactive protein (CRP), and interleukin-6 (IL-6)	(Haghighatdoost and Hariri, 2019)
LA for the treatment of disease related to central nervous system disease	• Various therapeutic potentials of LA such as anti-inflammation and antioxidant protection, scavenging reactive oxygen species, and regenerating other antioxidant agents • Potential of LA for the treatment of central nervous system disease	(Seifar *et al*., 2019)
Role of LA in female and male infertility	• Systematic review on evidence-based beneficial role of LA supplementation on male and female infertility	(Tucci *et al*., 2021)
Effect of LA supplementation on endothelial function	• Systematic review and meta-analysis on randomized controlled trials on the efficacy of LA supplementation on flow-mediated dilation (FMD) levels in adults • Significant increase in the levels of FMD was observed that varies with age and health status of the individuals	(Jalilpiran *et al*., 2021)
Effect of LA against viral infections including COVID-19	• Efficacy of LA against different viral infections • Beneficial effects of LA against SARS-CoV-2	(Dragomanova *et al*., 2021)
Mechanism of LA against neurodegenerative disorders	• A systematic literature review to study the mechanistic interventions of LA against diseases related to central nervous system • Changes in the expression of different proteins in mouse brain treated with LA	(Khan *et al*., 2022)
Effects of LA on metabolic syndrome	• Detailed discussion on the therapeutic activities of LA • Discussion on molecular mechanisms of LA against different components of metabolic syndrome	(Najafi *et al*., 2022)

to scavenge hydroxyl radicals and hypochlorous acid (Hassan *et al.*, 2017; Subramanian *et al.*, 2019); however, none of these forms were able to neutralize hydrogen peroxide.

It has been reported that DHLA has the potential to inhibit protein carbonyl formation by scavenging hypochlorite. In addition, DHLA regenerates potent antioxidants such as vitamin C and E (El Barky *et al.*, 2017), and has the potential to neutralize free radicals without getting involved in the process. It was observed that LA showed higher antioxidant activity in the cell culture study compared to *in vivo* study, probably owing to the direct reaction of LA with free radicals in the former (Shay *et al.*, 2009). Various researchers reported that, indirectly, LA regulates cellular antioxidants by two methods: (1) improving the synthesis of endogenous antioxidants with low molecular weight and antioxidant enzymes, and (2) inducing the uptake of the antioxidants at the cellular level (Kurutas, 2016). Reportedly, LA enhances the conversion of dehydroascorbic acid to ascorbate that was observed in the mitochondria of rat liver (Arivazhagan *et al.*, 2002). With age, rat cardiomyocytes revealed a decrease in ascorbate concentration, which was restored by dietary R-LA and reduced rat's oxidant production (Suh *et al.*, 2005).

GSH is a thiol-based natural antioxidant that acts as a co-substrate for detoxifying enzymes in various cells and tissues (Tibullo *et al.*, 2017). A study conducted by Packer *et al.* (1995) on human cell line and primary cells, such as erythrocytes, T cells, glial, lymphocytes, and neuroblastoma cells, reported the ability of LA to increase the GSH level. They have also reported that DHLA reduces the conversion of cystine to cysteine, which is the limiting substrate for GSH synthesis. Furthermore, LA may enhance cysteine concentration in cells by increasing cysteine absorption in plasma (Suh *et al.*, 2005). LA supplementation through diet has been successfully implemented for curing various diseases, such as diabetes and cardiovascular diseases, along with disease related to redox imbalance (Kurutas, 2016). However, detailed mechanism underlying these beneficial functions is required to be examined through *in vivo* and *in vitro* studies.

LA as metal chelator

Along with the potential to scavenge reactive species of oxygen, LA and DHLA showed chelating activity for redox-active metals at both *in vivo* and *in vitro* studies. The pair of oxidized and reduced forms of LA binds with

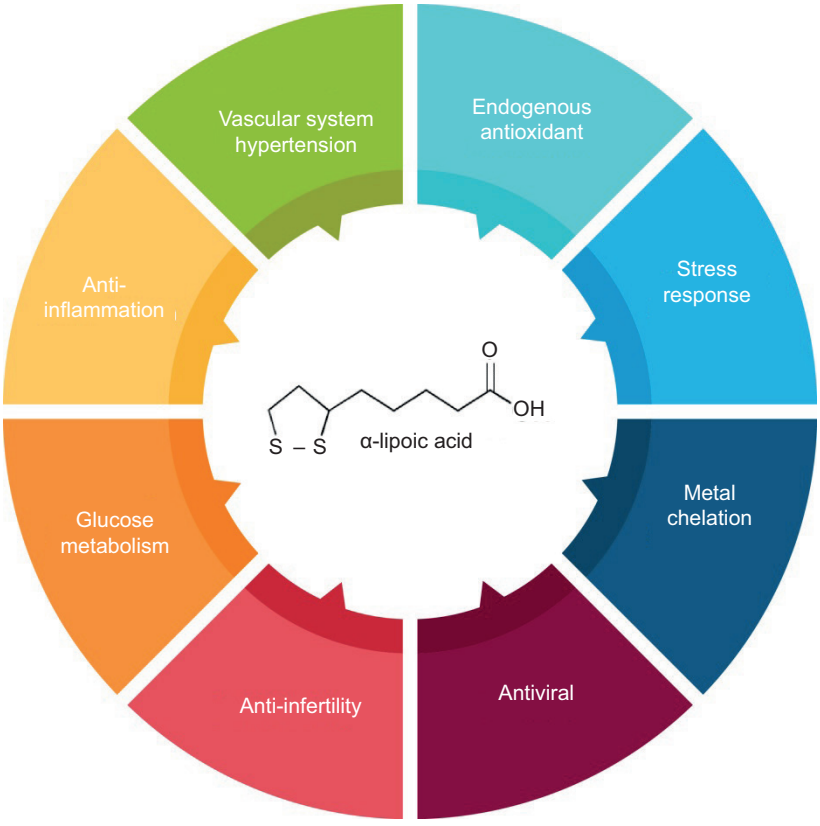

Figure 1. Various biological actions of α-lipoic acid.

various metal ions, after the metal chelation; the properties mostly depend on the chelated metal. These metal ions are responsible for several oxidative damages and catalyze different reactions that produce highly reactive free radicals. LA is one of the important compounds which helps in scavenging metal ions and prevents chronic diseases caused by the metal-induced oxidative damage (Goraca *et al*., 2011). Serhiyenko *et al.* (2018) reported that LA successfully binds with Cu^{2+}, Zn^{2+}, Mn^{2+}, and Pb^{2+} but is not able to chelate Fe^{3+}, whereas DHLA, in addition to these metal ions, forms a complex with Hg^{2+}, and Fe^{3+} *in vitro*. It was also reported that DHLA, in different concentrations, inhibited oxidation of Cu(II)(histidine)$_2$-mediated ascorbate *in vitro* but not LA; complete inhibition was observed when the molar ratio of DHLA: Cu(II) was 3:1 (Suh *et al*., 2005). Rochette *et al.* (2013) also reported similar results for *in vitro* prevention of Cu (II)-mediated oxidation of LDL.

DHLA plays a significant role in preventing Alzheimer's disease (AD) by binding with Fe^{3+} and Cu^{2+} in the brain that results in reducing the damage caused by the free radicals (Bush, 2002). A few studies have reported that DHLA inhibits metal-catalyzed free radical reactions by chelating transition metals in a redox-inactive way at the place of accumulation. Camiolo *et al.* (2019) have explored the iron chelating property of LA in human mesenchymal stem cells (HS-5) and observed that LA can reduce the chances of tissue iron accumulation, oxidative stress, and autophagy. Another study conducted by Kaur *et al.* (2009) reported that co-administration of LA and vitamin C provides protection against oxidative stress in liver and brain induced by arsenic. Furthermore, they concluded that combined administration of LA and vitamin C was more efficient compared to individual administration (Kaur *et al*., 2009). However, more *in vivo* and clinical studies are needed to understand the chelation effect of LA/DHLA in the human system.

LA as an inducer of endogenous antioxidants

Inflammation occurs when distinct vascular tissues respond to detrimental agents like irritants or pathogens. However, persistent chronic inflammation may lead to various diseases like asthma, rheumatoid arthritis, and atherosclerosis. Increase in the level of oxidative stress also supports the chronic inflammation that needs the initiation of NF-κB, a transcription factor that helps gene expression which is responsible for inflammation and endothelial cell migration. Keeping this as a research focus, LA was studied for prevention of cytokine-induced inflammation owing to its antioxidant potential, which also inhibits NF-κB activation (Ying *et al*., 2011).

LA is also experimented for reducing the expression of vascular cell adhesion molecule-1 (VCAM-1), and human monocytes endothelial adhesion, along with the prevention of NF-κB-dependent expression of metalloproteinase-9 *in vitro* (Kim *et al*., 2007), and the upregulation of intercellular adhesion molecule-1 (ICAM-1, in LA concentration range of 25–100 μg/mL), VCAM-1 in spinal cords, and in tumor necrosis factor-alpha (TNF-α) stimulated cultured brain endothelial cells (Chaudhary *et al*., 2006). Furthermore, LA has been reported for inhibiting osteoclast formation and bone erosion, and destruction of joint in rheumatoid arthritis (Kim *et al*., 2007).

LA as a hypertensive agent

Hypertension is responsible for heart attack, stroke, arterial aneurysm, and even chronic kidney failure. The use of LA for the prevention of hypertension showed increased GSH levels and inhibited harmful modification of sulfhydryl group in Ca^{2+} channels. It was observed that the supplementation of LA to rat with hypertension reduced systolic blood pressure and cytosolic free Ca^{2+}, as well as it reduced the development of renal vascular abnormalities (Louhelainen *et al*., 2006; Vasdev *et al*., 2005). Midaoui *et al.* (2002) and Laplante (2003) also reported the regeneration of GSH by LA, which is related to regenerating glutathione peroxidase activity when rats were fed with LA for regulating aortic superoxide generation and blood pressure.

Furthermore, dietary intake of LA prohibits surplus production of vascular endothelin-1, which is a vasoconstrictor secreted from endothelium (Takaoka *et al*., 2001). A recent study has also observed the enhancement of endothelial nitric oxide production by LA, which plays an important role as vasodilator in regulating the pressure in canal arteries (Shay *et al*., 2009). Furthermore, LA consumption with acetyl-L-carnitine, which acts as an anti-hypertensive agent, is responsible for reducing systolic pressure in hypertensive patients with metabolic syndrome (Long *et al*., 2009). However, thorough clinical trials, especially for the detection of dosage of LA for individual purpose, and combination of LA/DHLA with other nutraceuticals to enhance its potential are still required.

Degradation Mechanism of LA

Reportedly, the five-membered dithiolane ring of LA is easily decayed by photoirradiation, and simultaneously DHLA is generated. In this process, first diethyl radical is formed by the breakdown of disulfide bond, after that, formation of intra/intermolecular hydrogen bond leads to DHLA generation (Wada *et al*., 2009).

Bucher *et al*. (2005) conducted a study to examine the effect of laser flash on LA degradation and found production of carbon-centered radicals due to the breakdown of C-S bonds along with diethyl radicals (Figure 2). In addition, they have reported formation of DHLA by irradiation of ultraviolet C (UVC). Furthermore, their study emphasized that the degradation and regeneration of LA happens simultaneously under ultraviolet (UV) radiation. The transformation of radicals such as the thiol group by breakdown of S-S bond protects LA from degradation. The Thiol group has been previously used for the radical transfer reagent in the synthesis of polymers. Hydrogen abstraction converts DHLA into reduced LA ion through intermolecular cyclization. In addition, oxidized form of LA (DHLA) can be converted into the reduced form of LA in the presence of thiolate.

Thermal and light stability of LA can be enhanced by appropriate encapsulation of the compound. Researchers have conducted studies to enhance the bioavailability and stability of LA using different encapsulation techniques such as cyclodextrin-mediated inclusion complex, liposomal, and carbohydrate complexes (Table 3) (Ahmad *et al*., 2016).

Encapsulation Techniques for LA

Degradation of LA also produces undesirable odor owing to the release of sulfur compounds. Furthermore, LA exerts irritation on skin or mucosa owing to the acidic behaviors of carboxylic group when consumed directly. These issues along with difficulties in solubility, stability, and bioavailability make LA unsuitable for oral and external supplementation. To minimize these limitations, various formulations have been developed that possess distinctive physicochemical properties compared to pure LA, such as smaller size, high ratio of surface to mass, and enhanced reactivity (Table 3). The techniques used for encapsulation of LA have been discussed in this section.

LA inclusion complexes

Cyclodextrins (CDs) are cyclic oligosaccharides composed of repeating units of α-1,4 glucopyranose (Figure 3a). CDs have been reported for protecting the lipophilic food bioactives from oxidation, thermal- and photo-degradation along with the sustained release of active ingredients (Malegori *et al*., 2017). CD inclusion complexes have been used in various applications, such as medicine, environment, and other industries (Crini, 2014). In general, CDs require 6–8 glucose units to construct a cavity with different sizes that form a complex with different types of drugs (Li *et al*., 2007; Tian and Liu, 2020). The formation of this complex enhances the stability of the encapsulated drugs. In addition, studies reported that CDs inhibit oxidation and chemical changes of the encapsulated compound in the presence of oxygen (Pereira *et al*., 2021). Studies on LA inclusion complexes with different CDs evaluated the efficacy of the complex for thermal stability, light stability, and solubility of LA.

β-CD inclusion complex was examined to encapsulate LA by Raćz *et al*. (2012) (Figure 3b); in another study, the same complex was characterized using X-ray diffraction (XRD), differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), and nuclear magnetic resonance (NMR) (Raćz *et al*., 2013). The changes in vibration bands in FTIR spectra indicated the formation of inclusion complex. During the formation, the interaction between LA and β-CD increased the thermal stability of LA, evaluated by DSC study. LA inclusion

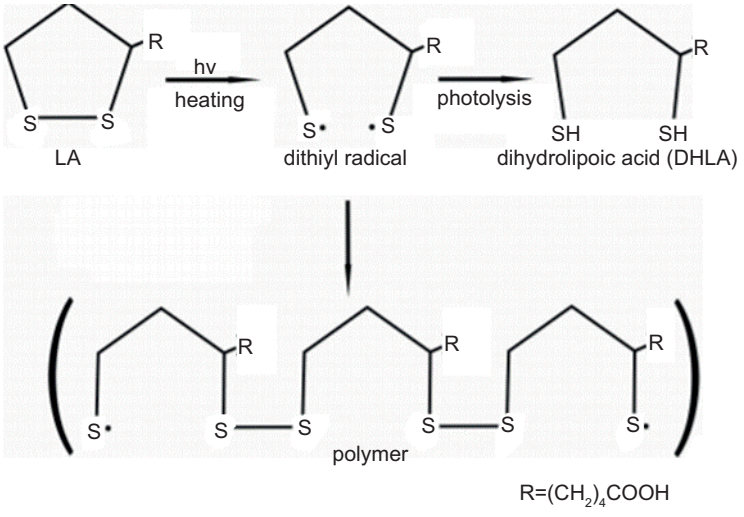

Figure 2. Schematic representation of products obtained from the thermal and photo degradation of LA (Dolinina *et al*., 2020).

Table 3. Different encapsulation techniques for α-lipoic acid

Encapsulating techniques	Encapsulating agents	Benefits/results	References
Spray drying	Chitosan	Spherical smooth particles with average particle size ranges from 3.53 to 7.89 µm Maximum encapsulation efficiency obtained was 55% Retention of antioxidant activity up to 75%	Weerakody *et al*., 2008
Nanostructured lipid nanocarrier	Octyl and decylglycerateglycerin monostearate and glyceride	Improved stability and water solubility Sustained release of LA was achieved Biocompatible to HaCaT cells	Wang and Xia, 2014
Inclusion complex	β-cyclodextrin	Complexed R(+)-alpha lipoic acid (LA) (RALA) has improved stability than free RALA under humidity, elevated temperature, and in acidic environment Shift in IR peaks due to complex formation	Ikuta *et al*., 2014
Polysaccharides gel beads	Alginic acid and chitosan	Enhanced stability against pH change Release of ALA was controlled through diffusion; mechanism in artificial gastric juice Enhanced stability against UV light and mild heat	Kofuji *et al*., 2009
Chitosan-coated liposome	Soy phosphatidylcholine; Cholesterol; Tween 80; Chitosan	Spherical shell core structure with particle size of 235 ± 2.3 to 308 ± 6.9 and zeta potential from 16.7 ± 1.07 to 30.2 ± 0.85 mV Reversion of surface charge to positive after coating with chitosan Bigger droplet size and enhanced stability Maximum encapsulation efficiency achieved was 91.28 ± 1.50%	Zhao *et al*., 2015
Single-capillary electrospraying	Poly (ethylene oxide) and chitosan	Spherical particles of 707 ± 66.68 nm diameter Positively electric surface potential of 57.7 ± 0.5 mV Prolonged release of LA up to 24 h Effective anti-inflammatory concentration was reduced significantly	Bai and Hu, 2014
Reverse emulsion cross-linking	Alginate/gelatin	Maximum encapsulation efficiency achieved was 53.9% In vitro release of LA was controlled after encapsulation Preservation of antioxidant activity of LA during storage period	Vidović *et al*., 2016)
Complexation using cation-exchange resins	Metformin HCl, Hydoxypropylmethylcellulose	Masked typical taste of LA Sustained release of drug for 10 h with first-order kinetics	Bhoyar and Biyani, 2010
Freeze drying	Calcium caseinate and sodium alginate, phytosterol ester of linseed oil and β-sitosterol	Maximum encapsulation efficiency of 84.32 ± 1.08% Irregular, rough surface of dried capsules Complete release of entire lipid happened within 210 min Maintained DPPH radical scavenging activity up to 36.95% after 90 days' storage period Metal chelation activity up to 39.29% after 90 days' storage period	Gupta and Ghosh, 2012
Solvent evaporated microemulsions	Poloxamer 188, coconut oil and egg lecithin	Spherical core shell of 243.7 ± 9.46 to 394.6 ± 4.05 nm Surface charge of −8.04 ± 0.48 to −1.8 ± 0.5 mV In vitro release of LA showed 96.28 ± 2.35% release in 4 h Beneficial for treating anemia	Mohamed Saliq *et al*., 2020
Solid lipid nanoparticle (W/O/W)	Coconut oil, jojoba oil, and macadamia oil, Tween 20 and Tween 60	Coconut oil showed highest encapsulation efficiency, i.e., 33.7% for 1% Tween 20 Particle size ranges from 200 to 300 nm SLN prepared with macadamia oil showed largest particle size Temperature and types of lipids have significant effect on release behavior	Kang *et al*., 2009
Inverse emulsion method	Chitosan microbeads	LA chitosan microbeads showed porous structure; spherical geometry and submicron size; encapsulation efficiency ranges from 46.8 to 58.5% Sustained release of LA under simulated gastric condition; reduced required dose of LA compared to immediate release doses	Milašinović *et al*., 2016

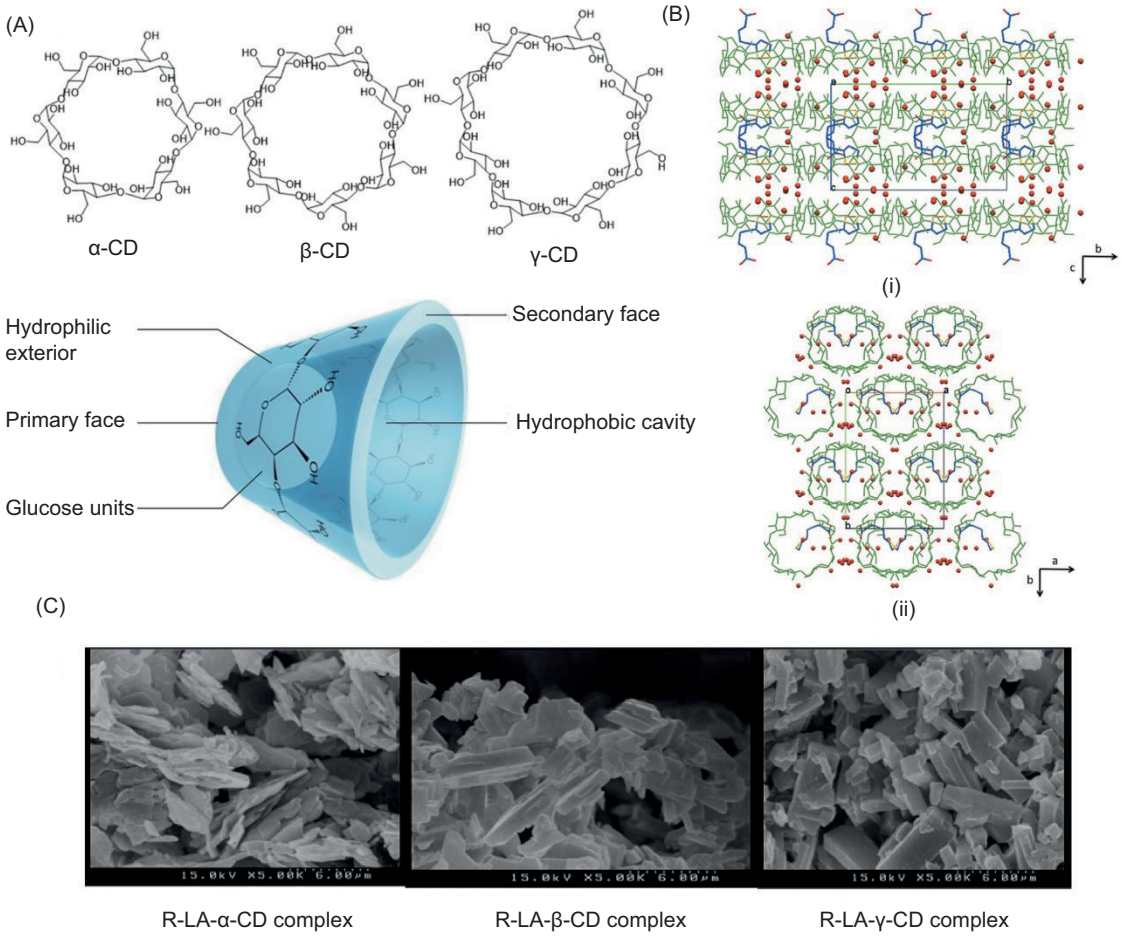

Figure 3. (A) The structures of α, β, and γ cyclodextrin (CD) (Tian *et al.*, 2020); (B) molecular packing of β-CD-LA inclusion complex: (i) along *a* axis, (ii) along *c* axis (Raćz *et al.*, 2012); (C) SEM images of complexes of R-α-lipoic acid (R-LA) and CD (Ikuta *et al.*, 2013).

complex showed the presence of both crystalline and amorphous phases in XRD pattern. From this study, inclusion complex was found to be beneficial in enhancing the absorption of LA. Figure 3c represents the visual morphologies of the complexes of radioligand assay (RLA) formed using three different forms of CD. Study conducted by Uchida *et al*. (2015) established an increase in absorption of RLA from inclusion complex compared to native RLA. It was observed that the absorption of RLA inclusion complex was affected by the types of CD used for the preparation of the inclusion complex. The authors investigated LA inclusion complexes with α, β, and γ-CD and their absorption pattern was examined in rat. Among all RLA complexes, γ-CD showed the highest exposure in plasma. The area under the plasma concentration-time curve (AUC) of RLA-γ-CD complex was 2.2 times greater than pure RLA after oral consumption. Contrarily, there was no difference in AUC when oral suspension was given to pylorus-ligated rats. However, intraduodenal administration of RLA-γ-CD showed 5.1 times higher AUC than pure RLA. These studies concluded that the RLA-γ-CD enhances the dissolution of RLA in small intestine lumen which leads to increased absorption in the intestine (Uchida *et al*., 2015). Another study also inferred the suitability of γ-CD inclusion complex for different formulations in the supplementation of RLA (Uekaji *et al*., 2012). According to the researchers, the increase in absorption may be because of the formation of micelles from γ-CD complex with bile acid and replacement of coenzyme Q10. However, bile acid showed no effect on the AUC (Uchida *et al*., 2015).

In another investigation, Maeda *et al.* (2010) prepared LA inclusion complex with modified CD for improving the solubility of LA in water. The authors used hydroxypropyl-β-CD (HP-β-CD), mono-6-O-glucopyranosyl-β-CD (mono-G1-β-CD), methyl-β-cyclodextrin (Me-β-CD), 2,6-di-O-methyl-β-CD (DMβ-CD), and sulfobutylether-β-CD (SBE-β-CD). Among all formulations, SBE-β-CD inclusion complex showed 20 times higher solubility than native LA (Maeda *et al*., 2010). Interestingly, the extent of formation of the

inclusion complex also depends on the mixing and drying processes. Researchers observed that the inclusion complex powders produced by kneading and freeze drying were entirely dissimilar to that produced by solid mixing process. LA formed inclusion complex with SBE-β-CD during kneading and freeze drying (not during solid mixing), and the retention of LA in these processes was 79 and 86%, respectively (Maeda *et al*., 2010).

Furthermore, inclusion complexes prepared from different starches, such as native high amylose (HA) and octenylsuccinylated high amylose (OS), are able to enhance the thermal and oxidative stability of LA to a greater extent compared to CD (Li *et al*., 2018). In addition, the OS was a more efficient stabilizing agent than HA. Release pattern of LA from different complexes demonstrated higher stability of OS complex at digestion condition compared to others. The formation of additional hydrophobic bonds between OS and LA is the major reason for the enhanced stability of LA in gastric conditions. Also, those hydrophobic interactions facilitated the formation of proper crystalline structure which enhanced the thermal and oxidative stability of LA (Zhang *et al*., 2011).

Spray drying

Spray drying is a well applied encapsulation technique for different food ingredients such as oils, fats, minerals, vitamins, and flavors to protect them from environmental degradation and to enhance their stability.

In an investigation, LA-chitosan microsphere was prepared using the spray drying technique with chitosan as the encapsulating agent that was able to encapsulate about 55% of LA. The scanning electron microscope (SEM) image of LA-chitosan microsphere showed a smooth surface, whereas chitosan microsphere without LA showed wrinkled geometry (Borghi *et al*., 2018). Surface area of the particle has an important role in the release behaviour of bioactive compounds from different delivery systems; smooth surface absorbs faster compared to particles with rough surfaces (Engstrom *et al*., 2007). However, to obtain high encapsulation efficiency, combinatorial application of encapsulation techniques could be utilized. Weerakody *et al*. (2008) observed interaction between the carboxylic group of LA and the amide group of chitosan during preparation of spray dried LA-chitosan microcapsules. This interaction altered the melting temperature of encapsulated LA. The combined effect of complex formation and spray drying process enhanced the stability of LA; moreover, it retained the antioxidant activity of LA and provided sustained release.

Another study was conducted by Eroğlu *et al*. (2017) for the preparation of poly(lactic-co-glycolic) acid (PLGA) microspheres of LA along with atorvastatin calcium (ATR) using the spray-drying technique. This formulation was especially prepared for the treatment of peripheral nerve injury in brain. SEM micrograph showed slight change in spherical geometry of the microspheres after loading of LA and ATR in PLGA. This change is probably the result of the increase in viscosity of solution which produced large droplets after atomization (Paudel *et al*., 2013), since a high viscous feed is difficult to be broken down into tiny particles (Anandharamakrishnan and Ishwarya, 2015). In another investigation, *in vitro* study described a fast release of LA from microspheres, whereas for ATR, the release was slow. *In vivo* study conducted using cell lines showed no toxic effect on neuron cells. Thus, the study established the effect of spray drying on the stability of LA and its functionality (Eroğlu *et al*., 2017).

Nanocapsules/microcapsules/beads

Nanotechnology provides unique physiochemical properties to the drug, such as formation of nanoscale particle, enhanced surface to mass ratio, and enhanced reactivity. Studies were conducted to develop LA nanocapsules using core shell structure of polyethylene (Vidović *et al*., 2016). TEM images showed spherical geometry of the particles. The nanocapsules were stable against aggregation in aqueous as well as in solid medium. Chitosan encapsulation of LA in microbeads is another method to inhibit the thermal degradation of LA, as well as to improve the sustained release of LA from encapsulates (Maleki *et al*., 2022). In a different approach, LA was incorporated into chitosan and alginate/gelatin, and cross-linked with zinc ions by reverse emulsion cross-linking technique. The encapsulation efficiency of LA in this system was 53.9%. *In vitro* release study demonstrated a controlled release of LA from chitosan microparticles; also the microparticles were able to retain the antioxidant activity of LA (Vidović *et al*., 2016). The swelling rate of chitosan microparticle was found to be increased owing to the generation of positive charge on the amino group of chitosan in gastric condition which leads to the development of repulsive forces between the polymer chains (Kim *et al*., 2003). With the increase in pH towards neutral, a hydrogen bond was formed and the swelling rate became constant. The fully swollen particle became stable and very useful for the delivery of LA; alginate microparticle showed significant swelling rate at higher pH due to neutral charge on the carboxyl group. At pH less than isoelectric pH, there was an increase in the hydrophilicity of the network and size of the hydrogel. In addition, increase in gelatin concentration showed no significant effect on the formation of hydrogen bond but reduced aggregation within hydrogel (Vidović *et al*., 2016). From this study, alginate was found to be very

efficient for enhancing the thermal and photo- stability of LA along with providing a sustained release.

The study conducted by Kofuji *et al*. (2008) demonstrated that alginic acid was able to enhance the stability of LA in addition to sustained release of LA from beads owing to the interaction of LA and chitosan (Kofuji *et al*., 2008). LA possesses negative charges with pKa in the range of 5.2 to 5.4, whereas chitosan possesses positive charge with pKa ranges from 6.2 to 6.5 (Ruixia *et al*., 2004). The interaction of LA and chitosan showed pH of 5.9 due to the high degree of ionization. A certain decrease in the degree of ionization of either compound leads to a change in pH and is responsible for the release of LA from chitosan. This is the reason behind the nonsustained release of LA from chitosan. However, formulations showed sustained release of LA when pH of dissolution medium was 1.20. In this pH, the amino group of chitosan gets ionized and interacts with carboxylic group of alginates; however, chitin, with the lesser amino group, did not interact with alginate in the low pH range and formulation showed sustained release of LA (Kofuji *et al*., 2008).

It was evidenced that antioxidant activity of compounds was enhanced by LA. Studies were conducted to encapsulate LA with other food bioactives to get synergistic effects of both compounds. Gupta *et al*. (2012) encapsulated LA along with β-carotene in lipid, and nanocapsules were produced using freeze drying. The emulsions were prepared using calcium caseinate and β-sitosterol, sodium alginate as wall material, and linseed oil as lipid phase. The maximum encapsulation efficiency achieved was 84.32 ± 1.08% for LA and 79.63 ± 1.41% for β-carotene. Morphology of nanocapsules observed by SEM revealed rough and irregular shapes of freeze-dried particles. The complete release of lipid from nanocapsules was recorded at 210 min (Gupta and Ghosh, 2012). However, the antioxidant activity of LA and β-carotene was found to be decreased during storage period.

In a different study, LA nanocapsules (LANCs) were prepared to fortify A2 cow milk. LANCs were prepared using poloxamer 188, coconut oil, and egg lecithin. Poloxamer and egg lecithin in the formulation were found to be responsible for enhancing the solubility and stability of LANCs. FTIR study demonstrated good compatibility of LA with other ingredients. The morphological study showed spherical arrangement of core and shell particle. The particle size and zeta potential ranged from 243.7 ± 9.46 to 394.6 ± 4.05 nm, and -8.04 ± 0.48 to -1.8 ± 0.5 mV, respectively. DPPH assay indicated the retention of antioxidant activity of LA in fortified milk samples. This formulation (LANCPs-fortified milk) was found to be able to enhance the blood count (RBC and Hb) of rats supplemented with fortified milk (Mohamed Saliq *et al*., 2020).

Lipid nanoparticles

Lipid nanoparticle can be prepared by various methods, such as high-pressure homogenization, solvent diffusion, microemulsion template, solvent injection, ultrasonication, solvent emulsification, reverse micelles double emulsion, cold homogenization, and membrane contactor methods (Baskar *et al*., 2021). SLN is one of the efficient delivery systems for bioactive compounds. It has several advantages, such as controlled release, enhanced activity, improved stability of bioactive compounds along with suitability for large scale production (Chen *et al*., 2012). However, there are few limitations associated with SLN, like leakage of active compound within a short span of time, and less loading of bioactive compounds. To overcome these limitations, nanostructured lipid carrier (NLC) was developed which is the modified form of SLN. SLN is produced from pure solid lipids, whereas NLC lipid component consists of incompatible liquid lipids mixed with solid lipid which provides more space for active compound and possesses various advantages over SLN, such as enhanced loading of active ingredients and suitability for accommodating other lipophilic active ingredients. Furthermore, NLC provides sustained drug release, biocompatibility, and feasibility to produce industrial scale products.

LA loaded NLC was found to enhance its stability, solubility in water, and achieve sustained release of LA (Wang and Xia, 2014). The LA-NLC was prepared with the help of homogenization technique. The biocompatibility and *in vitro* cytotoxicity of LA-NLC were evaluated using HaCaT cells by MTT assay, HE staining, and Hoechst 33342 staining. The average particle size of LA-NLC was 149.7 ± 5.4 nm and there was no significant effect of processing conditions on particle size. LA release behavior from LA-NLC during 72 h showed sustained release of LA, whereas pure LA released faster. The release of LA in the first 2 h from LA-NLC was 40.8%, whereas from pure LA it was 83.9%. The hydrophobic and electrostatic interactions play important roles in the sustained release of drugs from lipid nanoparticles. The strong electrostatic interaction between LA and lipid components leads to the deposition in lipid matrix which provides a sustained release of the drug from NLC (Chen *et al*., 2012). LA-NLC showed good biocompatibility with HaCaT cell lines and enhanced water solubility of LA.

The types of lipids used for the preparation of SLN play an important role in functional properties of SLN. Kang *et al*. (2009) used different types of lipids for the preparation of LA SLN (W/O/W) to achieve maximum encapsulation efficiency. Coconut oil, jojoba oil, and macadamia oil were used as lipid phase, and Tween 20 and Tween 60 were used as surfactants for the preparation of LA-SLN. The study demonstrated that SLN containing coconut oil

and 2% Tween 20 achieved highest encapsulation efficiency (33.7%) and smallest particle size. The release of LA from SLN prepared using coconut oil showed slow release possibly owing to the formation of compact structure formed by coconut oil. The release behavior was basically affected by the fatty acid content, hardness and, temperature of the lipid phase (Kang *et al*., 2009). The research conducted by Metwaly *et al*. (2022) established a higher efficacy of LA SLN compared to that of LA-chitosan nanoparticles against aluminum chloride–induced neurotoxicity in rats.

Electrospray technique

Electrospray (ES) has a wide application for the deposition of active compounds on thin films, for encapsulation, and polymeric particle deposition (Gupta and Panigrahi, 2020; Morais *et al*., 2020). During ES, high voltage is applied to the needle/nozzle loaded with the feed solution containing active molecules. At the edge of the tip, a liquid cone forms, releasing an array of monodisperse droplets. The droplet diameter depends on the conductivity, density, and flow rate of the feed solution. Thus, the resultant droplets are charged and need to be neutralized (Gupta and Panigrahi, 2020; Morais *et al*., 2020).

LA was encapsulated using single-capillary ES system by polyethylene oxide–chitosan (PEO-CS) as the encapsulating matrix. Results obtained from SEM and DLS demonstrated that ES can produce dry powder or water-based LA-PEO-CS particles with uniform size. Furthermore, a SEM study showed the spherical shape of LA-PEO-CS particle with diameter of 70.77 μm and DLS exhibited 734.50 nm diameter of suspended particle of LA-PEO-CS in water. In addition, zeta potential of LA-PEO-CS particles was 57.70 mV. Also, results demonstrated enhanced anti-inflammatory properties of LA-PEO-CS particles compared to pure LA owing to the efficient intracellular delivery. The ingress of LA-PEO-CS particle into LPS-treated Raw 264.7 macrophages revealed the electrostatic interaction with cell-surface molecules as the main driving force for ingress into the LPS layer and further proceeded by endocytosis of the attached particle (Bai and Hu, 2014).

Liposomal encapsulation

Liposome is a novel and multipurpose nano-delivery system for various bioactive materials. The distinctiveness of liposomes is its capacity to encapsulate both hydrophilic and hydrophobic bioactives (Du *et al*., 2015; Imran *et al*., 2015). Additional benefits of liposomes consist of their capability to retain the bioactivity of various compounds, enhanced bioavailability of bioactives at the cellular level, specific tissue or organ, the capacity to have either a positive or negative surface charge, high encapsulation efficiency, simple production methods, better stability during storage, and the stabilization of water-soluble bioactive compounds in a highly moist environment.

In a study, liposome-based formulation of coenzyme Q10 and LA was prepared for skin application. The liposome was further coated with chitosan to enhance its stability. The negatively charged liposome was easily coated by positively charged chitosan. Coated liposomes exhibited higher surface charge and particle size compared to uncoated ones. The increased zeta potential was responsible for the enhanced stability during the storage period. An FTIR study revealed that hydrogen bond and ionic bond between chitosan and LA favor the coating of the liposome. *In vitro* study demonstrated that this formulation possessed excellent hydroxyl radical scavenging activity and sustained drug release. Furthermore, this formulation was able to protect the skin by getting accumulated in the skin tissues (Wang *et al*., 2014).

In a different approach, Choudhary *et al*. (2021) encapsulated LA inclusion complex in chia oil nanoliposome to fortify cow milk (Figure 4). The maximum encapsulation achieved in the study was 80.24 ± 0.49% and 76.38 ± 0.58% for LA and chia oil, respectively. LA and chia oil nanoliposome fortified cow milk was able to supply 236.16 mg of LA and 719.52 mg of α-linolenic acid in a single serving (240 mL) of milk (Choudhary *et al*., 2021). In a recent investigation, LA has been encapsulated in liposomal formation with a mean particle size of 150 nm that successfully reduced plasma alanine aminotransferase and aspartate aminotransferase by 78.7 and

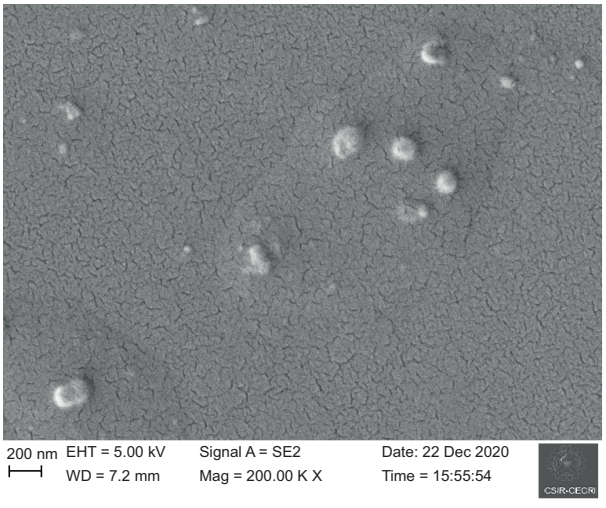

Figure 4. FE-SEM image of α-lipoic acid inclusion complex with HPβCD encapsulated in chia oil nanoliposome (Choudhary *et al*., 2021).

86.4%, respectively, in a rat model of acute hepatic injury (Halder *et al*., 2022). Thus, nanoliposome-based formulation is proven to be a very effective strategy to deliver LA at cellular level as well as for food fortification.

Challenges

Currently, the demand for functional foods in daily diets is increasing owing to the increasing health issues associated with poor lifestyle. LA is generally used in functional foods for controlling ageing, diabetes, and other diseases, and also for skin care. Encapsulation of LA enhances the bioavailability of the compound' however, there are few challenges associated with micro and nanoencapsulated LA that must be minimized before their industrial-scale implementation. The lack of regulation for LA-based functional food is the major obstacle for preparation, production, packaging, and distribution of these foods. Also, there is a lack of a detailed study about toxicological, ecological, and pharmaceutical aspects of nano/micro encapsulated LA. In addition, the fate of nanoencapsulated LA, along with encapsulating ingredients such as surfactants and cosurfactants, is another major apprehension. This issue can be overcome by considering the food and pharma-grade encapsulating ingredients such as soy lecithin, protein, and surfactants. As per the current research, there is no direct toxic effect of LA nanoparticles. Hence, FDA and Codex must provide proper regulations for the application of nanoparticles in food fortifications.

Summary and Future Trends

Different investigations on the encapsulation of LA have been discussed in the current review. The characteristics of each encapsulate vary with encapsulation technique and type of wall materials. From the literature, it is clear that the choice of encapsulation technique and wall materials depends on the kind of application of the encapsulates and the target site of the same. Highlights of the present review include the fact that encapsulation enhances the solubility, stability, and bioavailability of LA, *in vitro* as well as *in vivo,* compared to free LA. A thorough search of literature exhibits that although commonly used encapsulated techniques have already been investigated for the encapsulation of LA, still a few recent techniques, such as spray-freeze drying, spinning disk, extrusion, and refractance window drying have not been studied for the same. There is also a need to modify the methods of encapsulation and the coating material to enhance the encapsulation efficiency of each technique along with higher release of total LA from the encapsulates. Future research on LA encapsulation can also focus on the codelivery technologies in which two or more bioactive compounds can be delivered together to give a synergistic effect. Furthermore, a detailed study on health benefits of LA and the improvement of the same with encapsulation techniques needs to be conducted. In addition, the stability of encapsulated LA in different food systems has to be understood in detail.

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