Advances in Food Processing and Technology
Patil S, et al. Adv Food Process Technol 4: 127.
www.doi.org/10.29011/2639-3387.100027
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Review Article

Emerging Nano-Formulation Strategies for Nutraceutical Delivery

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Citation: Patil S, Chaudhari B, Acharya M (2023) Emerging Nano-Formulation Strategies for Nutraceutical Delivery. Adv Food Process Technol 4: 127. DOI: 10.29011/2639-3387.100027

Received Date: 08 August, 2023; **Accepted Date:** 17 August, 2023; **Published Date:** 22 August, 2023

Abstract

The global increase in consumer awareness of the benefits of natural ingredients has led to a paradigm shift in the health industry, with a focus on developing nutraceutical products. However, nutraceuticals often have poor oral bioavailability and stability, due to their poor solubility, chemical instability, and lower absorption, metabolism, and permeability. Nanotechnology has been used to address these challenges, with the development of various nano-technological approaches such as nanosponges, dendrimers, nanosuspensions, nanoemulsions, liposomes, nanohydrogels, carbon nanotubes, and solid lipid nanocarriers. These nanocarriers can protect nutraceuticals from harsh processing conditions, improve their solubility, and target them to specific tissues or cells. While nanotechnological approaches have the potential to improve the bioavailability and stability of nutraceuticals, more research is needed to assess their safety, efficacy, and regulatory acceptance.

Keywords: Nutraceuticals; Nanotechnology; Nanoliposomes; Solid-lipid nanoparticles

Introduction

Food or food components that provide health benefits beyond basic nutrition, such as preventing or treating diseases, are called nutraceuticals [1]. Consumer interest in nutraceuticals has grown due to their well-known health benefits and increasing demand for healthy and organic foods. This has led to a boost in the global nutraceuticals market. [2]. The steadily growing demand for dietary supplements and functional foods is a key driver of the global nutraceutical market. A Grand View Research report projects that the market will grow at a compound annual growth rate (CAGR) of 8-9% from 2020 to 2028. [3]. The COVID-19 pandemic has raised awareness of the importance of nutraceuticals, such as immune boosters, vitamins, antioxidants, and minerals. These products have been shown to be effective in meeting overall nutritional requirements. However, most nutraceuticals are unstable in light and air, which is a major hurdle to their widespread use. [4]. Different approaches are utilized to counter this hurdle, and this includes (i) the development and design new food matrices [5] and (ii) the use of encapsulation technologies [6]. Another problem with nutraceuticals is their solubility and pharmacokinetic properties, such as bioavailability, durability, and absorption. This review describes the use of different nanotechnology methods to overcome these issues [7,8]. (Figure 1).

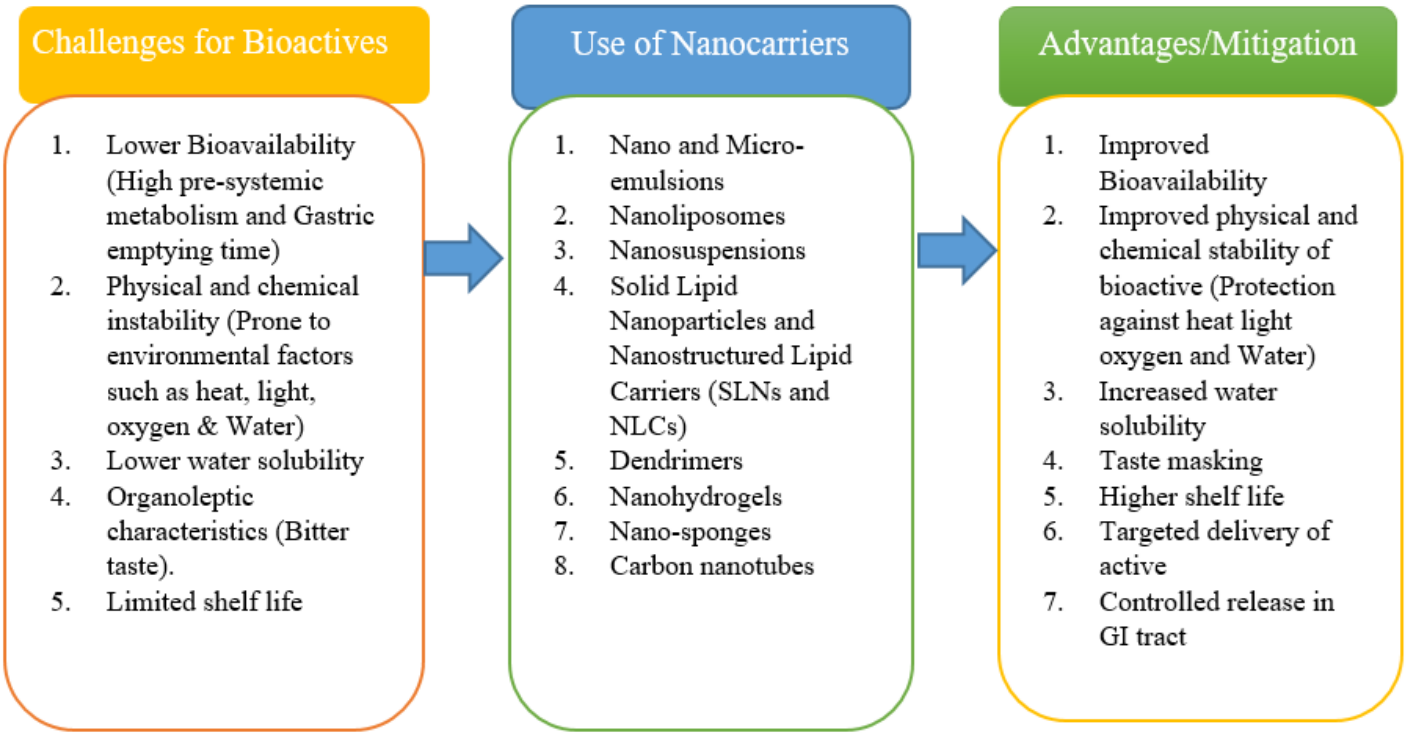

Figure 1: Shows the advantages of nanocarriers over bioactive challenges to improve the bioavailability of actives.

Nanoparticle-Based Delivery Systems

Nanoparticle-based delivery systems are promising encapsulation technologies for the industrial application of nutraceutical bioactives. Two types of nanoparticle-based systems are used: liquid and solid-delivery systems. Solid nanodelivery systems consist of three types of encapsulation: nanocrystals, lipid nanoparticles, and polymeric nanoparticles. Liquid nanodelivery systems consist of nanovesicles, nanoemulsions, and gas bubbles (foams, aerosols), which are dispersed in a continuous aqueous medium. These systems are discussed briefly in the following sections.

Dr. Norio Taniguchi introduced the term nanotechnology, which consists of generating and utilizing materials, mechanisms, or systems at a nanometer scale [9]. The U.S. National Nanotechnology Initiative describes nanoparticles (NPs) in the particle size of 1-100 nm [10-12]. The novel properties of nanomaterials offer many new opportunities for food processing, safety, and packaging [13]. Nanocarriers offer several advantages, including improved solubility, protection against oxidation, preservation of volatile bioactives, and protection of the encapsulated elements from environmental parameters such as oxygen, heat, water, and light. Additionally, nanocarriers can mask taste, improve stability, and extend shelf life [14]. Figure 2 describe the different nanoparticle based delivery systems or technologies used in nutraceutical product development. In recent years, several nanoparticle-based delivery systems, such as nanosponges, dendrimers, nanosuspensions, nanoemulsions, liposomes, nanohydrogels, and carbon nanotubes, have been extensively evaluated for their ability to improve the bioavailability and other quality attributes of nutraceutical bioactives. These nanoformulations can provide targeted delivery of the phytochemical and sustained release, in addition to improving bioavailability and therapeutic efficacy.

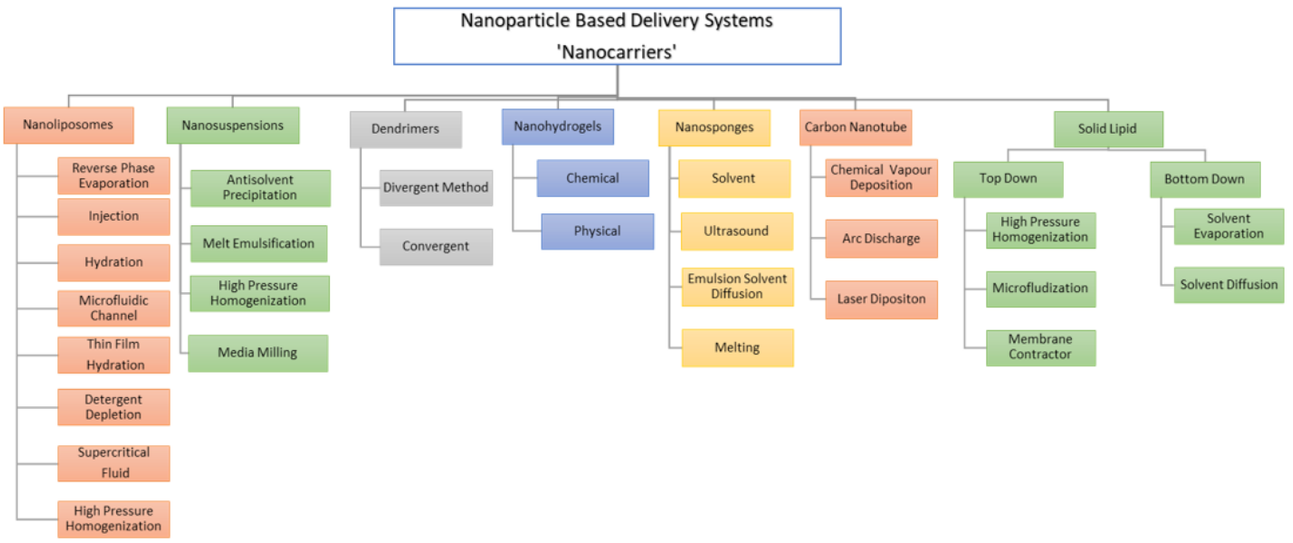

Figure 2: Schematic diagram of different Nanoparticle based delivery systems or technologies.

Nanocarriers are nanosized materials with a diameter of 1-100 nm that can carry multiple drugs and/or imaging agents. They play an important role in determining both *in vitro* and *in vivo* performance of bioactives, each with its own attributes. The selection of a specific nanocarrier depends on several parameters, such as the type of bioactives, their solubility, bioavailability, and target site. Nanocarrier systems consist of cores that can be liquid (emulsions and microemulsions), solid (solid lipid nanoparticles, or SLNs), or a mixture of solid and liquid domains (nanostructured lipid carriers, or NLCs). Particles for the encapsulation of hydrophilic bioactives are composed of an aqueous core surrounded by a shell that is distinct from the surrounding continuous phase. These include nanohydrogels, liposomes, and colloidosomes [15,16].

Poorly soluble bioactives are a challenging problem for formulators in the nutraceutical industry. Conventional approaches to solubility enhancement are limited in their applicability, especially when the bioactives are poorly soluble in both aqueous and non-aqueous media. Nanotechnology is a broad range of technologies, materials, and manufacturing processes that can be used to design and/or enhance many products, including medicinal products. This technology has achieved significant progress. Novel nanoformulations, such as nanoemulsions, nanosuspensions, liposomes, polymeric micelles, dendrimers, and gold nanoparticles, have been shown to enhance the delivery of bioactives and ultimately their bioavailability [17-20].

Nanocarriers

Micro and Nanoemulsions

An emulsion is a colloidal dispersion of two immiscible liquids, one of which is dispersed as tiny spherical droplets in the other. Emulsions are classified based on the relative spatial distribution of the oil and aqueous phases. Oil-in-water (O/W) emulsions are those in which oil droplets are dispersed in an aqueous phase. These emulsions can be used for the delivery of hydrophobic active substances. Water-in-oil (W/O) emulsions are those in which water droplets are dispersed in an oil phase. These emulsions are used for the delivery of hydrophilic compounds. [21-24]. Further, in the last few years, multiple emulsions have been investigated due to their importance in scientific applications. A Multiple emulsion is one in which the dispersed droplets contain even finer droplets of a different phase. Two types of multiple emulsions may exist including an oil-in-water-in-oil (O/W/O) emulsion and a water-in-oil-in-water (W/O/W) emulsion [25]. Emulsions can be classified into microemulsions and nanoemulsions based on their droplet size ranges. Microemulsions have droplet sizes in the range of 0.1-5 mm, while nanoemulsions have droplet sizes in the range of 20-100 nm and 5-50 nm. The ideal particle size for an emulsion depends on the methods of preparation, the type of emulsifier used, the target molecule, and the industrial application. [26]. Nanoemulsions have been extensively explored as drug delivery systems.

Over the past decade, nanoemulsions have gained popularity in food, beverage, and cosmetic products due to their potential advantages over conventional emulsions, which are associated with their smaller droplet size [27]. Nanoemulsions can be fabricated using a variety of techniques, which can be categorized as either low-energy or high-energy emulsification techniques. Low-energy techniques rely on spontaneous emulsification, which occurs when the surface tension of a mixture of oil, water, and surfactant is reduced by modifying the solution or physicochemical conditions. This results in the formation of tiny oil droplets. [28-30].

In the food industry, high-energy techniques are the most popular method for creating nanoemulsions. High-energy techniques are based on mechanical devices, which makes them easy to scale up and produce a high throughput. [27]. High-pressure homogenization is the most appropriate high-energy technique for creating nanoemulsions in the food industry. This technique involves forming an emulsion premix by mixing the oil, water, and emulsifier together using a high-shear mixer. The smaller size particles are then created by passing the mixture through a small orifice under high pressure. This generates intense forces that break large oil droplets into smaller droplets [31-34].

Microfluidization and ultrasonication are other high-energy techniques that can be used to create nanoemulsions. Microfluidizers use high pressure to convert larger emulsion droplets into smaller ones. The process involves passing a coarse emulsion through two separate channels under high pressure. The two channels meet at the end of the device, where the generated forces lead to the formation of smaller droplets. The final droplet size depends on the number of passes and the pressure applied. Jafari, et al. investigated the efficiency of microfluidization and ultrasound as emulsification techniques that produced nanoemulsions in sizes ranging from 150 to 700nm. Emulsions produced with Microfluidization provided a narrower droplet size distribution and sonication was more convenient in terms of operation and cleaning [35].

In ultrasonication, high-intensity ultrasonic waves create cavitation bubbles in the liquid. These bubbles oscillate rapidly and eventually implode, generating intense disruptive forces that break up the oil droplets into smaller emulsion droplets. [36]. Different Nanoemulsion technologies were used to improve the bioavailability of nutraceutical activities entitled in Table 1.

Sr. No	Formulation system	**Bioactive /Excipients**	**Health benefit/Treatment**	**Study type/ Purpose**	**Technique used**	**Characterization**	**Particle size**	**Study Outcome**	**Ref.**
1	O/W nanoemulsions	**Bioactive :** Gamma, alpha, and delta tocopherol, **Excipients** sodium pyruvate, polysorbate 80 and phosphatidyl choline	Inflammation	Nanoemulsions of an anti-oxidant synergy formulation (ASF) containing gamma tocopherol have enhanced bioavailability and anti-inflammatory properties	Microfluidization	Particle size, TEM	Suspensions: 673-843nm Nanoemulsions: 42.3-56.6	1. Nanoemulsions of ASF containing gamma, alpha, and delta tocopherol, have enhanced anti-inflammatory properties and increased bioavailability, with gamma tocopherol, in particular compared to their suspensions.	[115]
2	O/W nanoemulsions	**Bioactive :** Resveratrol, **Excipients:** whey protein isolate, gum Arabic, origanum oil, and polydatin, Fish and peppermint oil, Sunflower oil	antioxidant, anti-aging, inhibition of platelet aggregation, and anti-proliferative effects	Impact of oil type on the location, partition and chemical stability of resveratrol in oil-in-water emulsions stabilized by whey protein isolate plus gum Arabic	High pressure homogenization	Particle size, ζ-potential, surface protein percentage and concentration Partition of resveratrol	370-570nm	1. Emulsions containing sunflower oil, origanum oil, peppermint oil provided better protection on resveratrol against degradation than fish oil emulsions. 2. The effect of gum arabic on the polyphenol stability was dependent on oil type.	[116]

3	O/W nanoemulsions	**Bioactive :** lutein, **Excipients**: Food-grade soybean oil, Xangold 15% oil, vitamin E oil, Phospholipon 85G, Orange juice	Eye Health	Bioavailability of a Nanoemulsion of Lutein is Greater than a Lutein Supplement	Microfluidization	Particle size, polydispersity index	150nm	1. Nanoemulsions resulted in 31% ($P < 0.05$) and 28% ($P < 0.05$) greater serum lutein concentrations compared to the supplement. Nanoemulsions have greater bioavailability than lutein in a supplement pill form	[117]
4	O/W nanoemulsions	**Bioactive:** Curcumin, **Excipients**: hydrogenated phospholipid (Lecithin), rhamno lipids, Tween 80	Antioxidant, anti-microbial, anti-inflammatory, and anti-tumoral	Nano emulsions for Enhancement of Curcumin Bioavailability and Their Safety Evaluation: Effect of Emulsifier Type	High pressure homogenization	In-vitro Digestion, Particle Size, Polydispersity Index, and ζ-Potential, Free Fatty Acid (FFA) Release	144.1-176.1nm	1. Effect of Different emulsifier was studied. NE with Tween 80 - Lowest curcumin bio accessibility and stability. NE with Lecithin - Highest curcumin bio accessibility and stability	[118]

5	O/W nanoemulsions	**Bioactive:** Carotenoids in spinach, **Excipients**: Corn oil, Medium chain triglycerides, Bile salt, Powdered sodium caseinate,	Antioxidant	In-vitro and In-vivo study of the enhancement of carotenoid bioavailability in vegetables using excipient nanoemulsions: Impact of lipid content	High pressure homogenization	Particle size, ζ-potential, In- vitro digestion	d32:163-171 nm	1. Investigation of the impact of lipid content of excipient nanoemulsions on the bioavailability of carotenoids. 2. There was an increase in both bio accessibility (19.2% > 14.4% > 7.5% > 3.1%) and bioavailability (106.7 > 39.6 ≈ 35.3 > 15.0 ng/mL) of carotenoids with increasing lipid content (1.0, 0.6, 0.2, 0 g)	[119]

6	O/W nanoemulsions	**Bioactive** Vitamin D3 **Excipients:** Pea protein, soy lecithin and protein-lecithin	Vitamin deficiency status in aged population.	Pea protein-based vitamin D nanoemulsions: Fabrication, stability and in vitro study using Caco-2 cells	High pressure homogenization	Particle size, ζ-potential, Encapsulation efficiency Cellular uptake efficiency	170 to 350 nm	1. Protein-based nanoemulsions exhibited significantly higher cellular uptake than emulsions prepared using a combination of protein and lecithin. 2. The vitamin D transport efficiency across Caco-2 cells for small sized nanoemulsions (233 nm) was ~5.3 time's greater than free vitamin D suspension. 3. Research demonstrated that pea protein can be used as an effective emulsifier for preparing food nanoemulsions, which may enhance vitamin D bioavailability and improve vitamin deficiency status in aged population	[120]

7	O/W nanoemulsions (NE)	**Bioactive**: Long chain omega-3 Polyunsaturated fatty acid (LCn3PUFA) **Excipients :** Excipients: algal oil (Tocopherols and ascorbyl palmitate) L-□-Phosphatidylcholine, Tween 40	Nutrition	The composition and oxidative stability of vegetarian omega-3 algal oil nanoemulsions suitable for functional food enrichment	Ultrasound method	Droplet sizes, Oxidation and volatiles	NE with Tween 40 : 242 nm NE with Lecithin : 172 nm NE with Combination : 340nm	1. Oxidation compounds remained more stable at lower temperatures 2. NE with lecithin showed larger droplet size through 5-week storage trial. 3. NE combined with lecithin and Tween 40 showed lower droplet size at initial stage, however, increase in size observed t 40 deg and 5 weeks.	[121]
8	W/O/W double nanoemulsions	**Bioactive:** Ferula persica extract (FPE) **Excipients** : Locust bean gum (LBG) & Chitosan, Soybean oil, Complex of chitosan and LBG (CCL)	--	Incorporation of the Nano encapsulated polyphenolic extract of Ferula persica into soybean oil: Assessment of oil oxidative stability	High pressure homogenization	Particle size, ζ-potential,	76.61-147.91nm	1. The NE with combination of LBG and chitosan produced the best W/O/W nanoemulsion and followed by LBG and chitosan, respectively. 2. The FPE Nano encapsulated by CCL showed the best antioxidative activity in soybean oil.	[122]

9	O/W microemulsions (ME)	**Bioactive:** Lycopene **Excipients** : (R)-(þ)-limonene, Tween 80, Transcutol HP, polyethylene glycol 400, olive oil, glycerol, butylated hydroxytoluene, Soyabean oil, corn oil, Ethyl oleate, oleic acid	Neuroprotection	Oral delivery of lycopene-loaded microemulsion for brain-targeting: preparation, characterization, pharmacokinetic evaluation and tissue distribution	--	Particle size, ζ-potential,	12.61 ± 0.46 nm	1. Optimized composition: Lycopene, (R)-(þ)-limonene, Tween 80, Transcutol HP and water. 2. The pharmacokinetic study revealed 2.10-fold enhancement of relative bioavailability. 2. Lycopene ME showed preferential targeting distribution of lycopene toward brain in mice	[123]
10	W/O nanoemulsions	**Bioactive:** Fish Oil **Excipients** : Gum Arabic and Tween 80,	Cardiovascular Health	Use of Fish Oil Nano encapsulated with Gum Arabic Carrier in Low Fat Probiotic Fermented Milk	Ultrasound method	Particle size, Probiotic bacterial count, Peroxide content	36.67±1.33	1. Emulsion with Gum arabic (25%) and Emulsifier (2%) showed 1. Highest encapsulation efficiency (EE) and lowest Droplet side. 2. Increased the viability of Lactobacillus plantarum 3. Nano encapsulated fish oil in fermented milk significantly increased the viability of Lactobacillus plantarum	[124]

Table 1: Presents an overview of emulsion technologies used for different nutraceutical actives to improve the bioavailability of Bioactives.

Nanoliposomes

Liposomes are small, artificial vesicles that are made up of a phospholipid bilayer enclosing an aqueous core. They were first developed by Bangham, 1961, and have since been used in a variety of applications, including drug delivery, cosmetics, and food. Liposomes are typically made by dispersing phospholipids in an aqueous solution. The phospholipids spontaneously form bilayers, which enclose the aqueous solution in a vesicle. The size of the vesicles can be controlled by the method of preparation, and can range from a few nanometers to several micrometers in diameter [37]. When lipid and phospholipid molecules come into contact with an aqueous phase, such as buffers, they minimize contact with water molecules by forming bilayer structures known as liposomes or lipid vesicles. These bilayers encapsulate one or several aqueous spaces, forming a membranous system of colloidal particles [38-40]. With the advancement in nanotechnology, the phrase nanoliposome has been introduced to exclusively refer to nanoscale lipid vesicles, in nanometric size ranges [41].

Various liposomes are used for nutraceutical and pharmaceutical in-vivo and in-vitro applications. Based on their size and number of bilayers, liposomes can be classified into two categories: (1) Multilamellar vesicles (MLV) and (2) Unilamellar vesicles (ULV). MLV liposomes are like an onion structure, with several ULV encompassing one inside another of different sizes and making a multilamellar structure of concentric phospholipid spheres separated by layers of water. A liposome composed of many small, non-concentric vesicles encapsulated within a single lipid bilayer is called a multivesicular vesicle (MVV). The unilamellar liposome is a spherical, a vesicle, bound by a single bilayer of amphiphilic lipid or a mixture of such lipids, containing an aqueous solution inside the chamber and can be classified into two categories: (a) large unilamellar vesicles (LUV) and (b) small unilamellar vesicles (SUV). In unilamellar liposomes, the vesicle has a single phospholipid bilayer sphere enclosing the aqueous solution [42,43].

The techniques used for the preparation of liposomes are reverse-phase evaporation, injection, hydration, electroformation, microfluidic, thin-film hydration (Bangham method), freeze-drying of double emulsions, membrane extrusion, detergent depletion, heating method, etc., are well documented in the literature and explained below [44]. While preparation of liposomes it is observed that with lower payload of one or two%, lutein molecules placed in lipid bilayer in vertical position and remained stable during preparation, heating, storage, surfactant dissolution and showed less fluidizing properties. While with higher payloads of up to 5 and 10%, lutein molecules were placed vertically as well as horizontally in lipid bilayer. This arrangement displayed poor stability and weak retaining ability to lutein [45].

Reverse Phase Evaporation Method: The technique produces inverted micelles by dissolving lipids in an organic solvent by adding small volume of aqueous phase followed by sonication. Further, the organic solvent is removed using a rotary evaporator to form a viscous gel [46].

Injection Method: The ethanol injection method is a simple method for preparing liposomes. It involves dissolving the lipids in an organic solvent, such as ethanol or ether, and then injecting the lipid solution into an aqueous medium. The solvent then evaporates, leaving behind the liposomes. This method is simple and relatively easy to scale up, but some lipids are poorly soluble in ethanol, and heterogeneous liposomes may be formed if adequate mixing is not achieved. The ether injection method is similar to the ethanol injection method, but the ether is immiscible with the aqueous phase. This means that the ether can be easily removed from the liposomal product by heating, leaving behind a pure liposomal preparation [47,48]. Aafar-Maalej, et al., have used this method for the encapsulation of hydrophobic and hydrophilic bioactives, where they found higher encapsulation efficiencies observed at about 100% for the hydrophobic bioactive and about 16% for the hydrophilic. Also they found small multilamellar vesicles, with sizes ranging from about 80 to 170nm [49].

Hydration Method: The hydration method is a common method for preparing liposomes. It involves hydrating the phospholipid components in an aqueous solution containing 3% (vol.) glycerol. The temperature is then raised to 60°C or 120°C, depending on whether or not cholesterol is present. Glycerol is used because it is a water-soluble and physiologically acceptable chemical that can act as an isotonicity agent. It also increases the stability of lipid vesicles by preventing coagulation and sedimentation. [46].

Microfluidic Channel Method: Liposomes can be self-assembled in a microfluidic channel by passing a stream of lipids dissolved in alcohol between two aqueous streams. The lipids self-assemble into liposomes at the liquid interfaces, and the size distribution of the liposomes is governed by the laminar flow in the channels. This microfluidic method can be used to encapsulate bioactives immediately before use [50].

Thin-film hydration or Bangham method: The Bangham method involves dissolving lipids in an organic phase followed by evaporation removal of the organic solvent to form a lipid film. The final step was the hydration of the lipid film with an aqueous media or buffer was carried out in combination with agitation to separate the swelling lamellae from the vessel surface to form liposomes. This method generally produces liposomes with several microns in size, and consequently MLVs [46,51,52].

Detergent Depletion Method: The process is based on the formation of detergent-lipid micelles, followed by the removal of the detergent to form liposomes [53]. The initial ratio of detergent to phospholipid and rate at which the detergent is removed determines the size and homogeneity of liposomes [46,54].

Supercritical Fluid Method: Liposomes can be formed by dissolving lipids and cholesterol in supercritical carbon dioxide ($scCO_2$). The $scCO_2$ solution is then rapidly expanded into an

aqueous phase containing the hydrophilic compound to be entrapped. This method is called supercritical carbon dioxide ($scCO_2$)-assisted liposome formation. The encapsulation efficiency of this method is lower than that achieved using conventional liposome formation techniques. [55].

High-pressure Homogenization Method (HPH): In high-pressure homogenization (HPH), the sample is injected at high and constant pressure into a specially designed part of the homogenizer. The high pressure causes turbulence, cavitation, and shear phenomena, which rearrange the liposome structure. The number of cycles and pressure during the process determine the final properties of the liposomes [56,57]. An overview of liposome technologies used for different nutraceutical bioactives documented in Table 2.

Sr. No	Formulation system	Bioactive /Excipients	Health benefit/ Treatment	Study type/Purpose	Technique used	Characterization	Particle size	Study Outcome	Ref.
1	Pro-liposomes	**Bioactive**: Berberine **Excipients:** Hydrogenated soy phosphatidyl choline, sodium deoxycholate, mannitol, distearoylphosphatidyl glycerol, alphatocopherol,	cholesterol lowering and anti-hyperlipidemia	Berberine-loaded liposomes for oral delivery: Preparation, physicochemical characterization and In-vivo evaluation in an endogenous hyperlipidemic animal model	Air-suspension coating (layering)	size, distribution size, morphology, and entrapment efficiency	116.6 ± 5.8 nm	1. The oral bioavailability of Berberine Liposomes (Dose: 100 mg/kg) in rats was increased even 628% compared to that obtained with pure Berberine. 2. The BBR-loaded liposomes at the daily oral dose 100 mg/kg in P-407- reduced total cholesterol, triglycerides and low-density lipoprotein cholesterol (LDL-C) in hyperlipidemic mice by 15.8%, 38.2%, and 57.0%, respectively.	[125]
2	Liposomes	**Bioactive**: Extract of W. somnifera Dunal (NMITLI-118) **Excipients**: Soy phosphatidylcholine (soy lecithin) and egg phosphatidylcholine (EPC), cholesterol	Neuroprotection	Neuro-protective potential of a vesicular system of a standardized extract of a new chemotype of Withania somnifera Dunal (NMITLI118RT+) against cerebral stroke in rats	Thin-Film Hydration method	Mean particle size and poly dispersity index and zeta potential, encapsulation efficiency,Physical stability, neuro-protective potential	142.6 ± 0.09 nm	1. Both NMITLI118RT+ and its delivery system possess significant neuroprotective activity in cerebral ischemia. 2. The liposomal system largely exhibits better performance over NMITLI118RT+ precisely in the post-treatment group.	[126]
3	Liposomes	**Bioactive** : Carotenoid **Excipients** : Egg yolk phosphatidylcholine, Tween 80	Antioxidant activity	Liposomes as delivery systems for carotenoids: Comparative studies of loading ability, storage stability and In-vitro release	Thin-Film evaporation method	Carotenoid loading, Size measurement, Lipid peroxidation analysis, Storage stability, In-vitro release studies	With 2% IC: Lycopene - 67.37 ± 0.50 nm b-Carotene - 74.25 ± 1.01nm Lutein - 80.11 ± 0.52nm Canthaxanthin - 195.70 ± 7.32	1. Lipid peroxidation assay revealed incorporation of lutein or b-carotene exert strong antioxidant activity. 2. Liposomal membrane strongly retain b-carotene and lutein during storage, whereas this effect was not pronounced for lycopene and canthaxanthin. 2. In-vitro release studies demonstrated that lutein and b-carotene can display slow and sustained release in GI tract, whereas fast release appeared for lycopene and canthaxanthin.	[45]
4	Nanoliposmes	**Bioactive**: Quercetin **Excipients**: Phospholipids from Rice Bran, Soy Lecithin & Egg Yolk	anti-angiogenic activity	Enhanced bioactivity and efficient delivery of quercetin through nanoliposomal encapsulation using rice bran phospholipids	Thin Film & Sonication	Fatty Acid Profile of Rice Bran Phospholipids, Efficiency of Encapsulation, Particle Size and Morphology, Storage Stability of Nanoliposomal, Release Profile	157.33 ± 23.78 nm	1. Nanoliposomal quercetin showed a slow, limited release pattern in simulated gastric fluid (SGF) and an initial burst release followed by a slow constant releasing pattern in simulated intestinal fluid (SIF). 2. A 1004-fold increase in the 2,2-Diphenyl-1-Picrylhydrazyl (DPPH) radical-scavenging activity was observed in quercetin nanoliposomes, compared to non-encapsulated quercetin. 3. Anti-angiogenic activity of quercetin, as evaluated by duck embryo CAM assay, was enhanced two- to five-fold by nanoliposomal encapsulation.	[127]
5	Liposomes	**Bioactive:** Catechin and epigallocatechin-3-gallate (EGCG) **Excipients** : Soy lecithin	antioxidant properties	Delivery of green tea catechin and epigallocatechin gallate in liposomes incorporated into low-fat hard cheese	Homogenization	Particle size and zeta potential, SCryo-scanning electron microscopy, Transmission electron microscopy, Encapsulation efficiency, Encapsulation yield, Retention of liposomes in cheese and stability	133 nm	1. High efficiency (>70%) and yield (appox. 80%) were achieved with incorporation of catechin or EGCG. 2. Addition antioxidants increased the liposome phase transition temperature (>50 C). 3. Nanocapsules containing these antioxidants were effectively retained within a low-fat hard cheese, presenting a simple and effective delivery vesicle for antioxidants.	[128]
6	Liposomes	**Bioactive:** ascorbic acid **Exicipients** : soybean lecithin, Sterols (CardioAid-SWD and CardioAid-S)		Incorporation of phytosterols in soy phospholipids nanoliposomes: Encapsulation efficiency and stability.	high pressure homogenization	Average size, Encapsulation efficiency,release, Stability	115-150nm	1. Incorporation of plant sterols increased the vesicle size and their encapsulation efficiency. 2. This work clearly showed that, when preparing liposomes using high pressure homogenization, the presence of plant sterols affects their colloidal stability and encapsulation efficiency.	[129]
7	Liposomes	**Bioactive** : Vitamin A **Excipients** : Liposome: β-Lactoglobin-Liposome Complex: Phatidylcholine (PC from egg yolk)/ Cholesterol (CH)	Nutrient	In-vitro and In-vivo assessment of vitamin A encapsulation in a liposome-protein delivery system	Thin Film Dispersion & Freeze Drying	Encapsulation efficiency, Stability assessment, differential scanning calorimetry,	--	1. Phospholipid–sterol–protein membrane resembling system is one of the promising approaches to enhance Vitamin A absorption and to overcome the formulation difficulties associated with lipophilic means.	[130]
8	Nanoma gnetoliposomes	**Bioactive:** Curcumin **Exicipients**: Tween-60, ferric chloride anhydrous, ferrous sulphate heptahydrate, β-cyclodextrin, phosphate buffer saline (PBS) tablets, soya lecithin, cholesterol, glutaraldehyde	Antioxidant activity	Synergistic radical scavenging potency of curcumin-in-β-cyclodextrin-innanomagnetoliposomes	For Iron oxice NNP's - Microemulsion method Loading of Curcumin-in-β-CD complex into liposomes-Sonication and Centrifugation	Entrapment efficiency, Size distribution, XRD, FTIR, Radical scavenging assay, Morphology	67nm	1. Amount of curcumin used has a profound effect on morphology and stability of liposomes. 2. curcumin-in-β-cyclodextrin-in-nanomagnet liposomes is an effective strategy to enhance the tissue specific bioavailability of curcumin	[131]
9	Proliposomes	**Bioactive:** 6-Gingerol, Ginger extractive (10% gingerol) **Exicipients** :L-α-Phosphatidylcholine, cholesterol, sodium cholate and isopropyl myristate, Silica gel	Anti-tumor	A novel formulation of [6]-gingerol: Proliposomes with enhanced oral bioavailability and antitumor effect	Modified thin-film dispersion method	Encapsulation efficiency, In-vitro release, Particle size	44.77 ± 1.32 nm	1. In-vitro release of [6]-gingerol loaded proliposome compared with the free [6]-gingerol was significantly higher. 2. Oral bioavailability increased 5-fold In-vivo. Intriguingly, its antitumor effect was enhanced in the liposome formulation.	[132]
10	Liposomes	**Bioactive**: Cinnamaldehyde **Excipients**: Egg yolk phospholipid, Peptone, Beef extract, Tween 80	Anti-bacterial	Chitosan decoration improves the rapid and long-term antibacterial activities of cinnamaldehyde-loaded liposomes.	Ethanol injection Method	Encapsulation efficiency and retention rate, Particle size and zeta potential, Minimum inhibitory concentration,	Approx 300 nm with 2mg/ml of chitosan concentration	1. Chitosan and cinnamaldehyde exerted a cumulative and synergistic bacteriostatic effect in the liposomes which leads to damage the cellmembrane integrity, causing cell death. 2. This study provide guidance for the preparation and application of natural preservatives with rapid and long-term bacteriostatic effects.	[133]
11	Liposomes	**Bioactive**: Curcumin **Excipients**: L-α-phosphatidylcholine and L-α-phosphatidic acid	Ati-inflammatory, anticarcinogenic and antimicrobial properties	In-vitro digestion of curcumin loaded chitosan-coated liposomes	Reversed phase evaporation method	dynamic light scattering and zeta-potential measurements and surface charge	129nm	1. The presence of a positively charged surface (Chitosan bases coated) allows a better absorption of curcumin in the small intestine phase, which increases the overall curcumin bioavailability	[134]
12	Liposomes	**Bioactive**: citrus extract (CE) and essential oils (EOs) **Excipients**: Deoiled lecithin, fluidic lecithin		Preparation and characterization of natural extracts-loaded food grade nanoliposomes	Sonication Method	Encapsulation efficiency, Fourier-transform infrared spectroscopy (FTIR),	Nanoliposomes-CE : 95.6 ± 2.6 nm Nanoliposomes-EO : 102.2 ± 2.0 nm	1. Vesicle size of lecithin based nanoliposomes depends not only on the preparation technique but also on liposome composition especially considering saturated and unsaturated fatty acid composition. 2. Nanoliposome is a suitable technology for the nanoencapsulation of either hydrophilic or lipophilic bioactive extracts with sonication method.	[135]

Table 2: Presents an overview of liposome technologies used for different nutraceutical Bioactives.

Nanosuspension

Nanosuspension is a colloidal dispersion of pure, poorly water-soluble bioactives without any matrix material. Nanosuspension technology can improve the solubility, bioavailability, and pharmacokinetics of bioactives, leading to improved safety and efficacy [58].

Different manufacturing techniques can be used to produce nanosuspensions with uniform particle size and stability. The particles in nanosuspensions must remain unchanged in size throughout their shelf life, as otherwise they can initiate spontaneous crystal growth. Maintaining a uniform particle size distribution can help to prevent varying saturation solubility and inhibit crystal growth due to the Oswald ripening effect [59].

The preparation of nanosuspensions can be divided into two main methods: bottom-up and top-down. Bottom-up methods involve assembling nanoparticles from smaller units, such as anti-solvent precipitation, microemulsion, and melt emulsification. Top-down methods involve breaking down larger particles into nanoparticles, such as high-pressure homogenization and milling methods (media milling/dry grinding) [59-62].

Anti-solvent precipitation

The anti-solvent precipitation method works by rapidly producing nuclei and then controlling the growth rate of these nuclei. This method involves dissolving a bioactive in a suitable solvent, then rapidly mixing the solution with a solvent in which the bioactive is insoluble. The rapid addition of the solution to the insoluble solvent causes the bioactive to precipitate out of solution, forming ultrafine amorphous or crystalline particles [63,64].

Melt emulsification

The melt emulsification method is a bottom-up technique for preparing nanosuspensions. The particle size distribution of the nanosuspension is mainly affected by the concentration of bioactive, stabilizer, cooling temperature, and homogenization process. The process involves adding the bioactive to an aqueous solution with a stabilizer, heating the solution above the melting point of the bioactive, homogenizing the solution using a high-speed homogenizer, and cooling the suspension to precipitate the particles [65].

High-Pressure Homogenization

In High-Pressure Homogenization (HPH), the particle size of the suspension depends mainly on the number of cycles and pressure used during the process. In this method, a pre-suspension is prepared by dispersing the bioactive in a stabilizer solution and homogenizing it using a high-pressure homogenizer at low pressure for pre-milling. The pre-milled solution is then homogenized at high pressure with a different number of cycles until the nanosuspensions are formed with the desired particle size [66].

Media milling

In media milling, bioactives are subjected to high-speed milling to produce nanoparticles. The milling chamber is charged with the milling media, which includes the bioactive, stabilizer, water, or a suitable buffer. The milling media is rotated at a very high shear rate, which generates a suspension of nanoparticles. However, a significant problem with this method is that residues of the milling media can be left behind in the finished product [59,67].

In the dry milling method, stable nanosuspensions are prepared by dry grinding poorly soluble bioactives with soluble polymers and copolymers. The bioactives are first dispersed in a liquid medium, and then the mixture is dry ground using a high-speed mill. This process breaks down the bioactives into nanoparticles, which are then stabilized by the polymers and copolymers. Itoh et al. have described the use of this method to prepare nanosuspensions of many poorly water-soluble bioactives, including nifedipine, griseofulvin, and glibenclamide [68-70]. An overview of Nanosuspension technology used for different nutraceutical bioactives covered in Table 3.

Sr. No	Formulation system	Bioactive /Excipients	Health benefit/ Treatment	Study type/Purpose	Technique used	Characterization	Particle size	Study Outcome/Findings	Ref.
1	Nanosu spension	**Bioactive:** Lutein **Excipients** Soy phosphatidylcholine, Polyvinyl pyrrolidone, Mannitol,	Eye health	Improved oral bioavailability for lutein by nanocrystal technology: formulation development, In-vitro and In-vivo evaluation	anti-solvent precipitation-ultrasonication method followed by freeze-drying	Particle size and size distribution analysis Morphology, DSC and XRD studies, saturation solubility, Dissolution	110.7 nm.	1. The saturated solubility of lutein in water increased from 7.3 lg/ml for coarse powder up to 215.7 lg/ml for lutein nanocrystals. 2. The dissolution rate of lutein nanocrystals was significantly higher than that of coarse powder or the physical mixture. 3. The C_{max} and AUC_{0-24} h of lutein nanocrystals after oral administration in rats was 3.24 and 2.28 times higher than those of lutein suspension, respectively. These results indicated that the nanocrystal formulation c significantly enhance the dissolution and absorption of lutein	[136]
2	Nanosuspension	**Bioactive:** Curcumin (CUR) **Excipients** Polyvinyl pyrrolidone,	--	Particle size effect of curcumin nanosuspensions on cytotoxicity, cellular internalization, In-vivo pharmacokinetics and bio distribution	anti-solvent precipitation method	Particle size, zeta potential, Transmission electron microscopy, Atomic force microscopy, Dissolution study, Cytotoxicity, pharmacokinetics and tissue distribution of CUR in animals	20 - 200 nm	1. CUR-NS of (70- 200 nm) displayed stronger In-vitro bioactivity, enhanced cellular internalization and improved in-vivo bioavailability. CUR-NS of 70 nm showed better distribution in the lung and brain. 2. The particle size of the CUR-NS plays a key role in determining the bioactivity, pharmacokinetics and bio distribution of CUR.	[137]
3	Nanosuspension	**Bioactive: Curcumin Excipients** Protein β-lg,	--	Fabrication of amorphous curcumin nanosuspensions using-lactoglobulin to enhance solubility, stability, and bioavailability	anti-solvent precipitation method	Particle size, zeta potential and morphology analysis, Differential scanning calorimetry, X-ray diffraction	150–175 nm	1. The solubility of the amorphous curcumin nanosuspension was enhanced □35-fold due to the reduced size and lower crystallinity. 2. The amorphous curcumin nanosuspensions stabilized with β-lg and prepared at pH 3.4. 3. An In-vitro study using Caco-2 cell lines showed a significant increase in curcumin bioavailability.	[138]
4	Nanosuspension	**Bioactive :**Capsaicin **Excipients**: Carbopol 934, Tween 80/20,	Anti-inflammation	Fabrication of Capsaicin Loaded Nanocrystals: Physical characterizations and In-vivo Evaluation	top-down technique High speed Homogenization followed by Lyophilization	Droplet size, surface charge, poly-dispersibility index, bioactive content, entrapment efficiency, thermal analysis, surface morphology, solubility profile, In-vitro release and ex vivo permeation studies	120 ± 3.0 nm	1. The solubility of capsaicin was found to be 12.0 ± 0.013 µg/mL in water bioactive permeation was 68.32 ± 1.83%, bioactive retained in skin was 16.13 ± 1.11% while bioactive retained on skin was 9.12 ± 0.14% after 12 h. 2. The nanocrystals showed higher anti-inflammatory activity as compared to marketed product.	[139]
5	Nanosuspension	**Bioactive:** Hesperidin **Excipients**: Kolliphor1 P 188, Euxyl PE 9010 and glycerol.		Industrial concentrates of dermal hesperidin smart Crystals1 3 – production, characterization & long-term stability	wet bead milling and subsequent high pressure homogenization	Photon correlation spectroscopy, Laser diffractrometry, Zeta potential, Light microscopy, X-ray diffraction, Saturation solubility and chemical stability	250 nm	1. The saturation solubility of the nanosuspension was more than triple compared to the raw bioactive powder in water. Prepared Nanocrystals were stable over a period of 1.5 yrs with no change in particle size. 2. The smartCrystals1 CT method proved a versatile technology to produce Hesperidin concentrates.	[140]
6	Nanosuspension	**Bioactive :**Lutein **Excipients:** Plantacare® 2000 UP, Trehalose and lactose	antioxidant and anti-free radical	Lutein nanocrystals as antioxidant formulation for oral and dermal delivery	high pressure homogenization	Photon correlation spectroscopy, Laser diffractrometry, Zeta potential, Particle size	429 nm	1. Increase in saturation solubility by 26.3 fold. 2. In-vitro model, using cellulose nitrate membranes permeation was 14× higher for lutein nanocrystals compared to coarse powder.	[141]
7	Nanocrystals in oral films	**Bioactive :**Lutein **Excipients:** Soyphosphatidylcholine, sodium dodecyl sulfate, D-α-tocopherol polyethylene glycol succinate, Polyvinyl pyrrolidone, Tween 80,polyethylene glycol 400, Polyvinyl alcohol, Hydroxypropyl methylcellulose, Poloxamer 188, Cremophor EL	age-related macular degeneration.	Oral fast-dissolving films containing lutein nanocrystals for improved bioavailability: formulation development, In-vitro and In-vivo evaluation	Crystals : Anti-solvent precipitation method Films: Solvent casting method	Particle size, Morphology, Disintegration Test, Film Thickness Test, Determination of Folding Endurance, Differential Scanning Calorimetry, In-vitro Dissolution Study	377.9 nm	1. The C_{max} of nanocrystal OFDFs was 5.5- or 2.8-fold higher than that of lutein solution or conventional OFDFs, and the difference for AUC_{0-24}h was 2.1- or 1.6-fold. 2. The In-vivo evaluation in rats revealed that the application of film formulation improved the absorption rate and extent of lutein, and bioactive nanocrystal technology further enhanced the bioavailability of lutein.	[142]
8	Nanosuspension	**Bioactive:** Quercetin **Excipients:** Tween 80,	antioxidant activity	Preparation and Characterization of Quercetin Nanocrystals	High pressure homogenization	Photon correlation spectroscopy, laser diffraction, scanning electron microscopy, calorimetry, X-ray diffraction, dissolution test	483nm	1. Dissolution of the bioactive nanocrystals was much higher than that of the pure bioactive at pH 6.8 and 1.2 enhanced. 2. Dissolution rate was attributed to the increased effective surface area due to the decreased particle size, but not due to the presence of the amorphous fraction.	[143]
9	Nanosuspension	**Bioactive:** Apigenin **Excipients:** Plantacare 2000 UP® (alkyl polyglycoside)	antioxidant activity, anti-aging, Supportive to skin cancer protection	Production and characterization of antioxidant apigenin nanocrystals as a novel UV skin protective formulation	Bead milling and subsequently high pressure homogenization	Photon correlation spectroscopy, Laser diffractometry, Zeta potential, Light microscopy, X-ray diffraction, Free radical scavenging activity	413nm	3. Combination technology (Bead milling and high pressure homogenization) is very effective for formulation of poorly soluble apigenin. 4. In-vitro antioxidant activity almost doubled by creating a nanosuspension. This makes this formulation interesting for dermal application	[144]
10	Nanosuspension/ Nanocrystals in Gel	**Bioactive:** Rutein **Excipients:** Plantacare 2000 UP® ((alkyl polyglycoside))	antioxidant activity	Rutin—Increased Antioxidant Activity and Skin Penetration by Nanocrystal Technology (smartCrystals)	Bead milling and subsequently high pressure homogenization	Photon correlation spectroscopy, Laser diffractrometry, Zeta potential, Light microscopy, In-vitro Antioxidant Activity	214nm	1. The transfer of the µm-sized rutein raw bioactive powder into nanocrystals distinctly increase the In-vitro antioxidant activity of rutin. 2. Nanocrystals showed increased skin penetration. 3. These both effects are attributed to the increase in the saturation solubility by nanocrystal formation	[145]

Table 3: Presents an overview of Nanosuspension technology used for different nutraceutical Bioactives.

Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) are prepared from a lipid matrix having final particle sizes ranging between 50 and 1000 nm introduced in the early 1990's [71]. Solid Lipid Nanoparticles (SLNs) are important nanocarriers because of their large surface area, biodegradable and non-toxic lipid ingredients. They can enhance the bioavailability of hydrophilic and lipophilic bioactives, increase their physical stability, and allow for controlled release and targeting of bioactives. However, SLNs have some disadvantages, such as limited loading capacity, sudden expulsion of bioactive compounds due to phase transition upon storage, and relatively large water content [72-75].

There are two industrially feasible methods available for fabricating the SLNs specifically; (Figure 3) top-down or bottom-up methods. Some of the methods used in fabricating the bioactives loaded SLNs for food application are listed below [76-79].

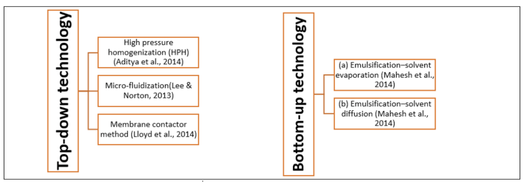

Figure 3: Methods used in fabricating the bioactives loaded SLNs for food application.

The method used to prepare SLNs depends on the physicochemical characteristics of the bioactive, payload, batch size, etc. The principles of all the methods mentioned above have been discussed in previous sections (nanoemulsions and liposomes). Among the methods mentioned above, High-Pressure Homogenization (HPH) and microfluidization are the most preferred technologies because they are easy to scale up and non-toxic. Table 4 summarizes the different SLN technologies used for different nutraceutical bioactives.

Sr. No	Formulation system	Bioactive /Excipients	Health benefit/ Treatment	Study type/Purpose	Technique used	Characterization	Particle size	Study Outcome/Findings	Ref.
1	Solid lipid nanoparticles	**Bioactive**: Berberine **Excipients:** tripalmitin, Tween 80 and poloxamer 407	Cardioprotection	Solid Lipid Nanoformulation of Berberine Attenuates Doxorubicin Triggered In-vitro Inflammation in H9c2 Rat Cardiomyocytes	water-in-oil microemulsion technique	Particle size, zeta potential, Entrapment efficiency, poly-dispersity index (PDI)	13.12	1. Ber-SLNs had a mean particle size of 13.12±1.188 nm, the zeta potential of -1.05 ± 0.08 mV, poly-dispersity index (PDI) of 0.317 ± 0.05 and entrapment efficiency of 50 ± 4.8% 2. Ber SLNs effectively prevented doxorubicin-induced inflammation and oxidative stress in rat cardiomyocytes	[146]
2	Solid lipid nanoparticles	**Bioactive**: Lutein **Excipients:** Gelucire® 44/14	Eye health	Lutein-Loaded Solid Lipid Nanoparticles for Ocular Delivery: Statistical Optimization and Ex Vivo Evaluation	hot homogenization and cold dilution method	Particle size, bioactive release, apparent permeability coefficient and steady-state flux, Corneal hydration	79.7	1. The optimized formulation showed mean particle size of 79.70 nm and sustained the bioactive release up to 8 h in simulated tear fluid. 2. The apparent permeability coefficient and steady-state flux of the optimized batch were found to be 1.09×10^{-6} cm/h and 7.33×10^{-3} µg/cm^2/h, respectively, and the corneal hydration was found to be 78.35%.	[147]
3	Solid lipid nanoparticles	**Bioactive:** Curcumin **Excipients:** polyoxyethylene(40)stearate (Myrj 52), ovalbumin (grade V), Stearic acid, lecithin chloroform, Tween® 80	Treatment of asthma	Enhanced bioavailability and efficiency of curcumin for the treatment of asthma by its formulation in solid lipid nanoparticles	solvent injection method	Particle size, zeta potential, X-ray diffraction, release profile, pharmacokinetics in tissue distribution	190 nm	1. The encapsulated curcumin formulation showed an average size of 190 nm with a zeta potential value of -20.7 mV and 75% bioactive entrapment efficiency and amorphous in nature. 2. The release profile of curcumin-SLNs was an initial burst followed by sustained release. 3. The curcumin concentrations in plasma suspension were significantly higher than those obtained with curcumin alone.	[148]
4	Solid lipid nanoparticles sunscreen system)	**Bioactive** : Tocopherol acetate **Excipients:** Cetyl palmitate, Tego Care1 450, Miglyol1 812, Glycerol, Xanthan gum	Sunscreen and skin care	A novel sunscreen system based on tocopherol acetate incorporated into solid lipid nanoparticles	--	Particle size examination, stability testing upon storage and thermoanalytical examination.	--	1. SLN dispersions showed at least twice as effective as their reference emulsions. Incorporation of tocopherol acetate into SLN leads to an over additive UV-blocking effect, improved sunscreen and skin care formulation.	[149]
5	Solid lipid nanoparticles	**Bioactive** : β -carotene and -tocopherol **Excipients:** stearyl ferulatebased solid lipid nanoparticles (SF-SLNs), as vehicles	Skin care	Stearyl ferulate-based solid lipid nanoparticles for the encapsulation and stabilization of -carotene and -tocopherol	Microemulsion technique at moderate temperature	Entrapment efficiency, size and shape together with their cytotoxicity and capability to inhibit lipid peroxidation	175.7 nm: SF-SLNs loaded with -tocopherol and 169.8 nm for SF-SLNs entrapping -carotene.	1. Study Results SF-SLNs provide a good vehicle for -carotene and -tocopherol as they are able to stabilize them, preventing the oxidation and the degradation of both compounds. 2. The cytotoxicity studies suggest that SF-SLNs are well tolerated at concentrations up to 5 µM, lower than SA-SLNs, in the formulation for short time exposure (no more than 6 h).	[150]

Table 4: Presents an overview of SLN technology used for different nutraceutical Bioactives.

Other Nano-Technological Approaches

Dendrimers

Dendrimers are a type of nanomaterial that have a tree-like structure. The term "dendrimer" was coined from the Greek words "dendron" (tree) and "meros" (part). Dendrimers are made up of a central core that is surrounded by branches. The branches are then further branched, creating a highly branched structure [80] These structures possess a unique potential in encapsulating/entrapping bioactive ingredients due to their tree-like nature[81].

Dendrimers possess a distinct molecular architecture that consists of three different domains: (i) a central core (ii) branches (iii) terminal functional groups, present at the outer surface of the macromolecule [82,83]. Dendrimers can be synthesized using a step-wise chemical synthesis approach. This approach allows for the preparation of dendrimers with specific sizes, structures, and low polydispersity index. Dendrimers are classified according to their generation number, which refers to the number of branching steps that have been carried out. For example, a G0.5 dendrimer has undergone one branching step, a G1 dendrimer has undergone two branching steps, and so on. The generation number of a dendrimer determines its size, structure, and properties. Dendrimers with higher generation numbers are larger and have more branches. They also have a lower polydispersity index, which means that they are more uniform in size. Dendrimers with higher generation numbers are also more complex and can be used for more applications [84].

The divergent method is a stepwise chemical synthesis approach for the synthesis of dendrimers. In this approach, the growth of a dendron originates from a core site, and the monomeric modules are assembled in a radial, branch-upon-branch motif. This method has the advantage of yielding a higher amount of dendrimer, but the purity of the product is lower [85].

The convergent approach to dendrimer synthesis was first introduced by Jean Frechet. In this approach, dendrons that end up in terminal groups are synthesized first. These dendrons are then linked to a core molecule in the final step to form a complete dendrimer structure. Dendrimers synthesized in this way have fewer impurities, more monodispersity, and symmetry because better purification of dendrons is possible before final attachment to the core. However, the size of the dendrimer synthesized by the convergent approach has limitations due to steric hindrance between dendrons attaching to a core. Overall, the convergent approach yields more uniform and symmetric dendrimers, but with a lower yield [86-88]. Research carried out on Dendrimer technologies with different bioactives documented in Table 5A.

Sr. No	Formulation system	Bioactive /Excipients	Health benefit/ Treatment	Study type/ Purpose	Technique used	Characterization	Particle size	Study Outcome/Findings	Ref.
1	Poly (amidoamine) dendrimers	**Bioactive**: Quercetin **Excipients**: Water-soluble poly (amidoamine) (PAMAM) dendrimer structure, Acetonitrile, o-phosphoric acid,	Diatery suppliment/ Treatment of inflammation	Evaluation of polyamidoamine dendrimers as potential carriers for quercetin, a versatile flavonoid	Entrapment of active in e inside a highly water-soluble poly(amidoamine) dendrimer structure	Solubility studies, Particle size analysis, Incorporation efficacy, Morphology .In-vitro release studies and Kinetics	34.39 to 100.3 nm	1. PAMAM dendrimers of different generations G0–G3 were found to have an appreciable effect othe n water solubility of quercetin. 2. Morphological studies revealed that the quercetin-loaded PAMAM complexes were spherical in shape and particle was size found less than 100 nm. 3. Prepared complexes showed sustained In-vitro quercetin release following patteren	[151]
2	Dendrimer-gold hybrid nano -structure.	**Bioactive**: Curcumin **Excipients**: Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, polyamidoamine dendrimer generation 5, EDC (1-ethyl3-(3-dimethylaminopropyl) carbodiimide hydrochloride), NHS (3-(4,5-and N-hydroxysulfosuccinimide), PEG polymer maleimide and carboxylic acid functional groups	Treatment colorectal adenocarcinoma	Curcumin-entrapped MUC-1 aptamer targeted dendrimer-gold hybrid nanostructure as a theranostic system for colon adenocarcinoma	PEG-Dendrimer conjugation : Freeze drying followed by synthesis and Encapsulation of curcumin in PEG-AuPAMAM-nanoparticles	Particle size, surface charge, In-vitro release of curcumin, Cellular uptake, n vitro cytotoxicity study, In-vivo CT scan imaging	2-4 nm in size	1. Homogenous spherical nanoparticles between 2-4 nm in size demonstrated that the synthesis of AuNPs are successfully controlled within the PEGPAMAM dendrimer as a template. 2. The release profile illustrated the sustained bioactive release up to 5 days in PBS pH 7.4. 3. higher cellular uptake, internalization, and cytotoxicity of Apt-PEG-AuPAMAM-CUR in comparison with PEG-AuPAMAM-CUR in C26 and HT29 cells. 4. In-vivo experiments showed the capability of the developed Apt-PEG-AuPAMAM-CUR hybrid structure as an effective anti-tumor therapy and accurate CT imaging of C26 tumorbearing mice	[152]
3	Poly (amidoamine) dendrimers	**Bioactive**: Ressveratrol **Excipients**: Water-soluble poly (amidoamine) (PAMAM) dendrimer structure.	Treatment and prevention of inflammation cancer, aging, Cardiovascular and neurological diseases	Dendrimer nanotechnology for enhanced formulation and controlled delivery of resveratrol	Entrapment of active in e inside a highly water-soluble poly (amidoamine) dendrimer stucture	--	1-10 nm	The dendrimer nanotechnology, owing to its multifunctional ability, has shown tremendous improvements in the aqueous solubility, stability, and pharmacokinetics of resveratrol.	[153]
4	Dendrimers	**Bioactive**: Apocarotenoids retinol and 8´-b-apocarotenol **Excipients**: Activated carboxylic acid derivatives, e N,N'-dicyclohexylcarbodiimide (DCC)/4-(dimethylamino)pyridine (¼ N,N-dimethylpyridin-4-amine; DMAP), Nnon-aromatic acids like benzenediyl- or triylacetic acids.	Eye Health	Towards Carotenoid Dendrimers: Carotenoid Diesters and Triesters with Aromatic Cores	Esterification	--	--	1. Aromatic di- or tricarboxylic acids proved to be unreactive. 2. Non-aromatic acids like benzenediyl- or triylacetic acids gave promising results and can form dendrimer structures. 3. The reaction of triol with carotenoid succinates gave low yields under identical conditions. In the case of retinol succinate, the yield was acceptable.	[154]
5	Poly (amidoamine) dendrimers	**Bioactive**: Curcumin **Excipients**: dendrimer PAMAM generation 5 (G5), triethylamine, acetic anhydride, V-APC, 7-AAD,	Treatment of cancer	Encapsulation of curcumin within poly (amidoamine) dendrimers for delivery to cancer cells	Partial acetylation of generation 5 PAMAM dendrimer (G5-Ac)	In-vitro Release Cell culture and cytotoxicity assay	--	1. Comparing with curcumin, the water-solubility value of G5-Ac/Cur increased 200-fold, and the release of curcumin from the complexes was sustained. 2. G5-Ac/Cur showed higher anti-proliferative activity against A549 cell lines and had the better effect on the generation of intracellular reactive oxygen species, the mitochondrial membrane potential and cell apoptosis	[155]

Table 5A: Research carried out on Dendrimer technologies with different bioactives

Nanohydrogels

Nanohydrogels are three-dimensional networks of hydrophilic or amphiphilic macromolecular chains that are cross-linked chemically or physically. They can hold a significant amount of water while maintaining their structure intact. The global market for hydrogels is expected to grow from $16.5 billion in 2017 to $22.3 billion by 2022, at a compound annual growth rate (CAGR) of 6.3% [89].

Nanogels are cross-linked networks of hydrophilic polymers that can be synthesized using either chemical or physical methods. They have a number of critical parameters, including their small size, viscoelasticity, swelling capacity, response to stimuli, and encapsulation stability. These properties make nanogels promising platforms for a variety of applications, including drug delivery, tissue engineering, and biosensing [90-92].

Different protein polymers (collagen, albumin and fibrin), polysaccharide polymers (chitosan, hyaluronic acid, heparin, starch, chondroitin sulfate, agarose and alginate), chitosan and fibrin can be used for the preparation of nanohydrogels [93-95]. Table 5B represent Research carried out on nanohydrogels technologies with different bioactive.

Sr. No	Formulation system	Bioactive /Excipients	Health benefit/ Treatment	Study type/Purpose	Technique used	Characterization	Particle size	Study Outcome/Findings	Ref.
1	Nanohydrogels	**Bioactive:** Curcumin and caffeine (As model bioactives based on solubility) **Excipients:** Lactoferrin-Lf, Glycomacropeptide-GMP,	Curcumin : antioxidative, anti-inflamatory caffeine : Increasing attention	Encapsulation and controlled release of bioactive compounds in lactoferrin-glycomacropeptide nanohydrogels: curcumin and caffeine as model compounds	Thermal gelation	Particle Size, polydispersity index, ζ-potential, Fourier transform infrared spectroscopy,Transmission Electron Microscopy, In-vitro release	112-126 nm	1. Curcumin and caffeine were successfully encapsulated in lactoferrin glycomacropeptide (Lf-GMP) nanohydrogels showing high encapsulation efficiencies (> 90 %).	[156]
2	Protein isolate-(WPI) hydrogels	**Bioactive:** Black carrot extract **Excipients :** WPI hydrogels, containing xanthan (XN), pectin (PC) and gum tragacanth (GT)	Antioxidant, anti-inflammatory and anti-tumorigenic	Encapsulation of curcumin in self-assembling peptide hydrogels as injectable bioactive delivery vehicles	Water bath (CV) and infrared assisted Microwave heating	Release and swelling experiments	--	1. Highest swelling ratio was observed at CV XN hydrogels and only XN hydrogels showed a distinct increase in swelling ratio (17.85%) with respect to WPI hydrogels containing no additional polymer (10.55%). 2. CV WPI hydrogels having no added polysaccharide showed the highest release percent (77.81%). MW increased the release rates of all polymer added hydrogels.	[157]
3	Hydrogel	**Bioactive:** Vitamin D3 **Excipients :** Chitosan, Alginate	Suppliment	Development of Hydrogels for Entrapment of Vitamin D3: Physicochemical Characterization and Release Study	Ultrasound	Efficiency of microencapsulation, loading capacity, mean particle size, Fourier transform infrared spectrometry, In- vitro release and release modeling	--	1. Optimal conditions for obtaining maximum microencapsulation efficiency (92.86%) and loading capacity (30.1%) are 0.23% alginate (W/V), 1: 5 weight ratio of vitamin D3: alginate, and 13.7 min ultrasound time. 2. Study showed the potential application of developed carriers to encapsulate hydrophobic compounds.	[158]
4	Sustain release Nanohydrogels	**Bioactive:** Lutein **Excipients :** Different concentrations of Ca2+, Sodium Alginate	Eye Health	Effect of Ca2+ cross-linking on the properties and structure of lutein-loaded sodium alginate hydrogels	--	Encapsulation efficiency, resilience, cohesiveness, Effect of different pH on swelling properties, DSC and FTIR	--	1. Highest loading capacity for lutein reached 770.88 µg/g, while the encapsulation efficiency was as high as 99.39%. 2. The resilience and cohesiveness of the hydrogel decreased as the concentration of Ca2+ increased. 3. DSC and FTIR results showed that lutein nanoparticles were mainly physically trapped in the hydrogel network structure.	[159]
5	Hydrogel	**Bioactive:** Vitamin D3 **Excipients:** Sodium Alginate, Calcium carbonate and D-glucono-δ-lactone.	Wound dressing in skin tissue engineering.	A promising wound dressing based on alginate hydrogels containing vitamin D3 cross-linked by calcium carbonate/D-glucono-δ-lactone	--	Microstructure, swelling behavior, weight loss, hemo-cytocompatibility and therapeutic efficacy of the fabricated hydrogels	--	1. The SEM images showed that hydrogel was highly porous (89.2 ± 12.5%). 2. The prepared hydrogel is biodegradable with the weight loss percentage of about 89% in 14 days and were hemo- and cytocompatible. 3. This study suggests that alginate hydrogels with 3000 IU vitamin D3 can be exploited as a potential wound dressing in skin tissue engineering.	[160]

Table 5B: Research carried out on nanohydrogel technologies with different bioactive.

Nanosponges

Nanosponges are a type of nanoparticle that are often synthesized on a carbon-containing polymer. They have a porous structure with pores that are about 1-2 nanometers in size. This makes them ideal for targeting and absorbing small amounts of matter or toxin. One of the key advantages of nanosponges is their ability to enhance the chemical and physical stability of the incorporated bioactives. This protection from degradation can help to design delivery systems for nucleic acids, peptides, proteins, and sensitive small molecules. In addition to their stability, nanosponges are also biocompatible and biodegradable. This makes them a promising platform for a variety of applications, including drug delivery, tissue engineering, and biosensing [96]. Curcumin and resveratrol are two compounds with low solubility and poor bioavailability. They have been co-administered in a number of nanodelivery system formulations, including encapsulation in pyromellitic dianhydride cross-linked β-cyclodextrin-based nanosponges. A topical formulation was also prepared using a bioactive-loaded nanosponge dispersed in a carbomer-based hydrogel. This formulation led to a remarkable increase in the photostability of the compounds. In vitro cytotoxicity studies on MCF-7 cells showed that the combination of curcumin-loaded nanosponges and resveratrol-loaded nanosponges had a synergistic effect [97].

There are several methods of preparation of NSs; (i) solvent method, (ii) ultrasound assisted synthesis, (iii) emulsion solvent diffusion method, and (iv) melting method. Out of which solvent method and emulsion solvent diffusion methods are most commonly used.

The solvent method for synthesizing nanosponges (NSs) involves adding a cross-linker to a mixture of polymer and a polar aprotic solvent, such as N,N-dimethylformamide or dimethylsulfoxide. The molar ratio of cross-linker to polymer is 4:16. The reaction mixture is then heated for 1 to 48 hours at a temperature ranging from 10°C to the reflux temperature of the solvent. Once the reaction is complete, the mixture is cooled to room temperature and poured into an excess amount of distilled water. The NSs are then recovered by filtering the mixture under vacuum. They can be further purified by soxhlet extraction, if necessary. To encapsulate bioactive molecules, the same procedure is followed after the formation of hollow NSs. The bioactive molecules are dissolved in the solvent before adding it to the reaction mixture [98].

The ultrasound-assisted synthesis method for synthesizing nanosponges (NSs) uses ultrasonic waves to cross-link the polymer without any solvent. The polymer and cross-linker are mixed in an appropriate molar ratio and then subjected to an ultrasound bath for 5 hours at a temperature of 90°C. After sonication, the mixture is cooled and the solid mass is broken up roughly. It is then washed with an excess amount of water to remove unreacted polymer and reagents. The washed solids are purified by Soxhlet extraction with ethyl alcohol. The obtained purified NSs are dried under a vacuum and stored until further bioactive loading [99,100].

The emulsion solvent diffusion method for synthesizing nanosponges (NSs) uses the principles of emulsification. In this method, a solution of bioactive and polymer in a suitable volatile solvent is mixed with an aqueous emulsifier solution, such as PVA in water. The two phases are immiscible, so they form an emulsion. The internal phase is added dropwise to the external phase with constant stirring until the solvent in the internal phase evaporates. This creates minute pores in the NSs [101,102].

The melting method for synthesizing nanosponges (NSs) involves homogenizing all of the ingredients, including the cross-linker and polymer. The mixture is then heated with continuous stirring for a long time, followed by cooling. The NSs are collected by repeatedly washing the obtained mass. The anti-angiogenic activity of quercetin was enhanced by two NSs, as evaluated by the duck embryo CAM assay. These unloaded blank NSs were further subjected to bioactive loading [103]. Overview of Nanosponges technology used for different nutraceutical bioactives covered in Table 5C.

Sr. No	Formulation system	Bioactive / Excipients	Health benefit/ Treatment	Study type/ Purpose	Technique used	Characterization	Particle size	Study Outcome/Findings	Ref.
1	Nanosponges	**Bioactive**: Quercetin **Excipients:** β-cyclodextrin and diphenyl carbonate	Antioxidant activity	Fabrication of cyclodextrin nanosponges for querctin delivery: Physicochemical charac- terization, photostability, and antioxidant effects	freeze-drying method	Size distribution and polydispersity index, ζ-potential, Fourier transform infrared spectroscopy, X-ray diffraction, Raman spectroscopy, differential scanning calorimetry, Transmission Electron Microscopy, In-vitro release	40 - 100 nm	1. The particle sizes of plain and quercetin-loaded nanosponges are in between 40 and 100 nm with low polydispersity indic es. Zeta potential is sufficiently high to obtain a stable colloidal nanosuspension. 2. The dissolution of the quercetin nanosponges was significantly higher compared with the pure bioactive. 3. The antioxidant activity of the quercetin nanosponges was more effective than pure quercetin on DPPH scavenging, anti-superoxide formation, and sExcipientsnion scavenging.	[161]
2	Nanosponges	**Bioactive**: Curcumin **Excipients:** Cyclodextrin, Dimethyl carbonate	Tumor treatment	Cyclodextrin-based nanosponges of curcumin: formulation and physicochemical characterization	--	Size distribution The amount phosphatidylcholine index, solubility studies, ζ-potential, Fourier transform infrared spectroscopy, X-ray diffraction, In-vitro release	487.3 nm	1. The loaded nanosponge was shown more solubilization efficiency (20.89 µg/ml) in comparison with plain curcumin (0.4 µg/ml) and β-CD complex (5.88 µg/ml). 2. The zeta potential was sufficiently high (−27 mV) which indicates formation of a stable colloidal nanosuspension. 3. FTIR, XRD and DSC studies confirmed the interactions of curcumin with NS. 4. The In-vitro bioactive release of curcumin was controlled over a prolonged period of time Performance to hemolysis study showed that the complex was non-hemolytic.	[162]
3	Nanosponges	**Bioactive**: Thyme essential oil (TEO) **Excipients:** β-cyclodextrin, Diphenyl carbonate	Antimicrobial and antioxidant activity	Incorporation of thyme essential oil into the β-cyclodextrin nanosponges: Preparation, characterization and antibacterial activity	--	Size distribution, scanning electron microscope (SEM), Fourier transform infrared spectrohigh-pressure, X-ray diffraction, Encapsulation efficiency, loading capacity, solubility, and antibacterial properties, In-vitro release	326 nm	1. FTIR and XRD confirmed the incorporation of TEO into the nanosponges. 2. The inclusion complex of TEO into the nanospongesincreased its antibacterial activity. 3. The aqueous solubility of TEO was enhanced by 15-folds after encapsulation within nanosponges. 4. Minimum inhibitory concentration of TEO was decreased up to 29.4 folds after encapsulation into the nanosponges.	[163]
4	Nanosponges	**Bioactive**: Resveratrol **Excipients:** Cyclodextrin, carbonyldiimidazole	--	Cyclodextrin-based nanosponges for delivery of resveratrol: In-vitro characterization, stability, cytotoxicity and permeation study	--	Size distribution, polydispersity index, ζ-potential, Transmission electron microscope (SEM), Fourier transform infrared spectroscopy (FTIR) , X-ray diffraction, In-vitro release	400-500nm	1. DSC, FTIR and X-ray powder diffraction (XRPD) studies confirmed the interaction of resveratrol with NS with low polydispersity indices. 2. Zeta potential is sufficiently high to obtain a stable colloidal nanosuspension. 3. The In-vitro release and stability of resveratrol complex were increased compared with plain bioactive . 4. Cytotoxic studies on HCPC-I cell showed that resveratrol formulations were more cytotoxic than plain resveratrol. 5. The permeation study indicates that the resveratrol NS formulation showed good permeation in pigskin.	[164]
5	Nanosponges	**Bioactive**: Curcumin (CUR) and Caffeiene (CFN) **Excipients:** β-cyclodextrin, Diphenyl carbonate, carbopol-934, Guar gum	Curcumin : anti-inflammatory caffeine : antipsoriatic action	Design & development of nanosponge loaded topical gel of curcumin and caffeine mixture for augmented treatment of psoriasis	hot melt method	viscosity and Vitro percent bioactive release, In-vivo animal studies,	--	1. The optimal formulation showed 69.72% In-vitro bioactive release and 12,329.78cp viscosity. 2. Histopathology studies revealed that prepared nanogel has promising anti-psoriatic activity. 3. The results concluded that CUR and CFN combination has reduced the time required for showing anti-psoriatic activity to 10 days when compared to CUR alone that took around 20 days. Moreover, the nanogel has depicted sustained bioactive release till 12 h.	[165]

Table 5C: Overview of Nanosponges technology used for different nutraceutical bioactives.

Carbon Nanotubes (CNTs)

Carbon nanotubes (CNTs) are a type of nanomaterial that have played a significant role in nanotechnology and material science. CNTs are tube-like structures made up of carbon atoms. They are classified based on the number of carbon layers that they contain. CNTs can be thought of as a graphite sheet that has been rolled up into a cylinder. The graphite sheet is made up of benzene rings, which are arranged in a hexagonal lattice. CNTs have a number of unique properties, including high electrical conductivity, high thermal conductivity, and high mechanical strength. These properties make CNTs attractive for a variety of applications, including electronics, energy storage, and composites. [104,105].

Single-Walled Carbon Nanotubes (SWCNTs) consist of a single graphene layer with a diameter varying between 0.4 and 2 nm and usually occurs as hexagonal-packed bundles. Multi-Walled Carbon Nanotubes (MWCNTs) comprises two or several cylinders made of graphene sheets. The diameter varies from 1 to 3 nm [106,107]. Chemical vapor deposition, electric arc and laser deposition method were used to fabricate carbon nanotubes [108]. Carbon nanotubes exhibit various characteristic properties such as high elasticity, high thermal conductivity, low density and they are chemically more inert etc.

Chemical Vapor Deposition (CVD) is a method for synthesizing carbon nanotubes (CNTs) that involves decomposing a carbon-containing gas at high temperatures in the presence of a metal catalyst. The catalyst is the most important factor that determines the morphology, structure, and properties of CNTs. Other important factors include the carbon source, substrate, and processing conditions. The most common catalysts for CVD synthesis of CNTs are iron, cobalt, nickel, and molybdenum. These metals are typically deposited on a substrate, such as a silicon wafer, and then the carbon-containing gas is introduced into the chamber. The gas is decomposed at high temperatures, and the carbon atoms are deposited on the catalyst surface, where they form CNTs [109,110].

The arc-discharge method is the cost-efficient technique for synthesizing carbon nanotubes where an arc is generated between two graphitic rods kept at a certain distance of a few mm. The time required for CNT synthesis is also less as compared to other methods [111,112].

Laser deposition is a method for synthesizing carbon nanotubes (CNTs) that involves sublimating graphite using a high-intensity laser beam. This method produces high quality and high-purity CNTs, but it is also very expensive. The quality of CNTs produced by laser deposition is affected by a number of factors, including the type of catalyst, laser power and wavelength, temperature, pressure, type of inert gas, and the fluid dynamics near the carbon target.

The catalyst is used to initiate the growth of CNTs. The most common catalysts for laser deposition are iron, cobalt, nickel, and molybdenum. The laser power and wavelength determine the temperature at which the graphite is sublimated. The temperature, pressure, and type of inert gas affect the growth rate and morphology of CNTs. The fluid dynamics near the carbon target affect the uniformity of CNT growth. Laser deposition is a versatile method for synthesizing CNTs with a wide range of properties. It is a scalable method that can be used to produce large quantities of CNTs. However, the high cost of synthesis limits its use in commercial applications [113,114]. Carbon nanotubes technology used for different nutraceutical bioactives explained in Table 5D.

Sr. No	Formulation system	Bioactive /Excipients	Health benefit/ Treatment	Study type/Purpose	Technique used	Characterization	Particle size	Study Outcome/Findings	Ref.
1	Single-walled carbon nanotubes (SWCNTs)	**Bioactive:** Curcumin **Excipients:** functionalized SWCNTs, Glycomacropeptide-GMP,	Anti-cancer	Formulation of curcumin delivery with functionalized single-walled carbon nanotubes: characteristics and anticancer effects In-vitro	Conjugation of functionalized SWCNTs with curcumin (SWCNT-Cur).	Size distribution, ζ-potential, Morphology,Solubility, stability X-ray diffraction and release of curcumin	170.4 nm	1. SWCNT-Cur conjugates showed significantly enhance the solubility and stability of curcumin. 2. Conjugates are in amorphous form and could be rapidly released. In PC-3 cells, improved inhibition efficacy was achieved by SWCNT-Cur compared with native curcumin.	[166]
2	Multiwalled carbon nanotubes (MWCNTs)	**Bioactive:** Berberine **Excipients:** polysorbate and Phospholipids	Anti-Alzheimer	Anti-Alzheimer's potential of berberine using surface decorated multi-walled carbon nanotubes: A preclinical evidence	Conjugation of functionalized MWCNTs with Berberine	Particle size distribution, bioactive adsorption amount of bioactive released in 16h, Degree of carboxylation, FTIR, FESEM and vivo pharmacokinetic studies in rats	186 nm	1. Optimized formulation exhibited particle size of 186nm, 68.6% bioactive adsorption, amount of bioactive released in 16h (Q16h) of 96% and Degree of carboxylation was observed to be 36%. FTIR and FESEM studies confirmed the coating of polysorbate and phospholipid onto the MWCNTs side walls. 2. In-vivo pharmacokinetic studies in rats showed significant improvement in the rate and extent of bioactive absorption in the plasma and brain tissues, both, vis-a-vis pure bioactive	[167]
3	Carbon Nanotubes (CNT's), gold nanoparticles (GNPs), carbon nanotubes and gold nanoparticles (CNTs-GNPs) Electodes as biosensor	**Bioactive:** Green Tea (Catechin) **Excipients:** polysorbate and Phospholipids	Anti-oxidant	Assessment of the Antioxidant Activity of Catechin in Nutraceuticals: Comparison between a Newly Developed Electrochemical Method and Spectrophotometric Methods	Electrodes were modified with the laccase (Lac) enzyme, using glutaraldehyde as a cross-linking agent between the amino groups on the laccase and aldehyde groups of the reticulation agent.	Oxidative properties using cyclic voltammetry (CV) and differential pulse voltammetry (DPV) and catechin content using biosensors	--	1. Catechin content estimated using biosensors was in agreement with the manufacturer's specification.	[168]

Table 5D: Overview of carbon nanotubes technology used for different nutraceutical bioactives.

Conclusion

The functional food market has grown in recent decades due to increased consumer demand for natural, nutritional, and healthy food products and supplements. The growth of the market for nutritious foods and dietary supplements is driven by the rising awareness of preventive healthcare and the current lifestyle. Nanoscale delivery systems (NDDS) have the potential to be a valuable tool for formulation scientists in overcoming many formulation and delivery challenges related to the physicochemical properties of plant bioactives (such as protecting them from light, oxygen, or pH changes). The development of NDDS for use in the nutraceutical and food sectors is expected to continue due to their advantages over other delivery systems, particularly nanoencapsulation. Other key features that NDDS can incorporate to improve clinical effectiveness include improved bioavailability, increased solubility, enhanced permeability, modified release characteristics, and higher stability of plant bioactives. However, considerable attention must also be given to limitations such as high payloads, acceptable daily intakes, safety, and regulations. This review investigated different NDDS used for the protection and delivery of nutraceuticals, along with the manufacturing method, characterization, applications, and their suitability for plant bioactives. Some researchers have proposed novel ingredients in combination with NDDS, which have shown promising results in delivering health benefits. Both in vitro and in vivo studies have shown that the oral bioavailability of lipophilic nutraceuticals can be significantly increased using NDDS. However, some critical challenges that need to be addressed for the successful commercialization of nano-based products include solid-state behavior, high payload, encapsulation efficiency, long-term stability, in vivo release behavior, and the interaction between bioactive ingredients and multiple encapsulating carriers. Furthermore, regulatory frameworks and guidance are needed that adequately address and specifically manage the potential risks of nanotechnology. Several countries around the world have been active in assessing the suitability of their regulatory frameworks for dealing with nanotechnologies.

Acknowledgements

The authors are grateful to Research and Technology department, OmniActive Health Technology, Thane, India for their bursary support.

Conflicts of Interest/Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' Contribution

All author has equal contribution to the writing of the manuscript.

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