



## Review Article

# Encapsulation of Hydrophobic Bioactive Substances for Food Applications: Carriers, Techniques, and Biosafety

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Biologically active substances (BASs) are used as novel ingredients to design functional foods. These functional foods are alternate approaches to treat or cure chronic diseases. However, the application of BASs is limited due to their hydrophobic nature, low bioavailability, sensitivity to gastric acid, and environmental conditions (i.e., high temperatures, radiation, pH, and oxygen). Thus, research has been channeled to find ways of curbing these limitations. This review provides an overview of the modern methods for BAS encapsulation, carrier classifications, benefits, and drawbacks as well as the biosafety of encapsulated BASs. Encapsulation of BASs into organic/inorganic carriers or composites overcomes the limitations mentioned above. In addition, encapsulation enables the controlled release of active compounds to target cells. The market for encapsulated foods has grown globally at a significant pace due to their various applications as functional foods, dietary supplements, and other products. It is estimated that by 2027, the market worth of encapsulated foods will be valued at \$17 billion.

## 1. Introduction

Biologically active food additives (BAFAs) are either natural or artificial biologically active substances (BASs) used to enhance nutritional values of plant- and animal-based food products in a form of functional foods [1]. BASs have been reported to exert numerous biological activities (i.e., antioxidant, anticancer, anti-inflammatory, antiangiogenic, neuroprotective, and antiobesity) of health benefits on humans [2, 3]. BASs are generally hydrophobic, chemically unstable in food system, and prone to degradation, especially when exposed to oxygen, light, humidity, and high temperature [4]. For example, the oxidation of phenolic compounds can develop unpleasant tastes and off-odors in food products, thus negatively influencing the shelf life and organoleptic features [1]. Therefore, encapsulation is considered as a feasible alternative to preserve the quality of BASs and enhance their applicability in the food industry [5].

Encapsulation is a process of incorporating bioactive compound (core material) into external shell commonly referred to as a carrier material [6]. It is a promising technique used to preserve the nutritional value [7], improve solubility [8, 9] and oxidation stability of active ingredient [10, 11]. The carrier, an encapsulating agent (also known as external phase, wall material, shell, or matrix) is used to shield BASs (designated as internal phase, active agent, or core) from light, oxygen, pH, moisture, heat, shear, or other extreme conditions (gastric juice) in a form of capping or coating [5]. The carriers protect the BASs from the harsh environment conditions until their controlled release, thus enhancing bioavailability [12]. It is reported that a carrier material must adhere to carefully selected desired release criteria [13]. Globally, as of 2022, the value of food encapsulation market is \$11.4 billion and is expected to increase by 2027 to \$17 billion. This market is dominated by the US due to health awareness, the need to prevent chronic diseases

coupled with promotion of lifestyle by patronizing nutraceutical and functional foods [14]. Other key players, mostly developed countries, include Germany, Ireland, The Netherlands, UK, Switzerland, Australia, Israel, and Italy [15]. Surprisingly, no developing countries made the list partly due to the cost involved in the research and development of encapsulated foods.

Encapsulation methods such as electrospinning [16], electrospraying [17, 18], spray drying [19, 20], microfluidics [21, 22], extrusion, 3D printing [23], coacervation [24], lyophilization [25], incorporation into nanotubes [26], porous micro-/nanospheres [27, 28], nanocomposites [29, 30], isoelectric precipitation [31], antisolvent coprecipitation [32], and ionic gelation [33] introduce hydrophobic phenolics, alkaloids, oils, vitamins, food colorants, and flavors into carriers without altering their chemical and biological properties. In addition, encapsulation masks unpleasant tastes and flavors in food, thereby increasing consumer satisfaction of a product. Therefore, this review highlights the recent advancements in encapsulation and biosafety of encapsulated BASs in the food industry.

## 2. Carrier Classification

Carbohydrates, proteins, lipids, and other organic and inorganic materials are used as carriers during encapsulation of BASs [5]. However, carrier material must meet certain criteria to be suitable for engineering encapsulation systems. Some of the criteria include the following characteristics (Table 1): (1) structural: composition and phase state; (2) functional: solubility, viscosity, particle size, morphology of the surface, and total charge of particles; (3) organoleptic: color, flavor, and aroma; (4) physicochemical: resistance to changes in pH, temperature, humidity, oxidizing agents, and radiation; (5) physiological: release mechanism, conformational changes in the gastrointestinal tract (GIT), release rate, and toxicity; (6) economic: financial availability of materials and technologies; (7) cultural, religious, and food restrictions [34, 35].

Carriers can further be divided into several groups (Figure 1) based on their morphological structure [36], phase state of substances [37], and nature of the material [36].

**2.1. Organic Carriers.** Natural polymers are preferred materials for encapsulating bioactive food compounds due to their unique characteristics such as nontoxicity, edibility, and biocompatibility. Organic carriers can be subdivided into 4 groups, namely, (1) lipids, (2) carbohydrates, (3) proteins, and (4) their composites: protein + protein, polysaccharide + polysaccharide, and protein + polysaccharide (Table 2) [4]. For instance, a lipid-based carrier can be a single oil/water (O/W), water/oil/(W/O), or double O/W/O, W/O/W emulsions, and liposomes which consist of a single or double layer of phospholipids. Encapsulation in liposome is one of the most popular methods of using lipids as the main wall components [5]. Lipid carriers can be used to encapsulate lipophilic (i.e., carotenoids and essential oils) and hydrophilic (i.e., water-soluble vitamins and flavonoids)

bioactive compounds [43–46]. Nanostructured lipid carriers showed good physical stability, adjustable particle size, and controlled and extended release of bioactive compound [47].

Natural polysaccharides, notably starch [48], cellulose [49], chitosan [50], inulin [51], dextrin [52], hyaluronic acid [53], fucoidan [54], and pectin [55], are used as substrates to synthesize amphiphilic polysaccharides via octenylsuccination [56], acetylation [57], and esterification with fatty acids [58]. In addition, semisynthetic polysaccharides with grafted hydrophobic groups and synthetic polysaccharides had attracted attention as wall materials [59].

Chitosan, a cationic polyelectrolyte is widely applied in pharmaceutical and food industries due to its unique properties, such as mucoadhesiveness, nontoxicity, biocompatibility, biodegradability, and extractability from economically advantageous sources [60]. Chitosan is water-soluble and positively charged at lower pH and thus forms complexes with negatively charged molecules, such as gum Arabic (GA), carboxymethyl cellulose, alginate, and heparin [61]. Many studies have explored the interactions of chitosan with biopolymers or ions, to design particles/capsules loaded with BASs (Table 2).

Animal-derived proteins (whey protein isolate [62], whey protein concentrate [24, 63], soy protein isolate [63], egg protein [64], collagen [65], gelatin [63, 66], zein (corn protein) [16, 67, 68], and casein [69]) were successfully used as a carrier materials to encapsulate BASs, despite their allergenicity [4]. The demand for eco-friendly and vegan products forges the path for plant-based proteins as wall materials coupled with their abundance in nature, low cost, and less allergenicity [70].

The potential capsule formation from aqueous solutions of dextran, maltodextrin, resistance starch, pullulan, fructooligosaccharides, whey protein concentrate of milk, and soy protein isolate was investigated [71]. Among the materials, only dextran, pullulan, and whey protein formed capsules about 1 mm in size. The sprayability differences were associated with the low viscosity coupled with high surface tension values. Nevertheless, soy protein with high molecular mass ( $M_w$  30,000–350,000) was not a suitable material due to strong inter- and intramolecular forces that hindered chain entanglement [71]. The authors further explored electrospraying which denatured soy protein and improved the intermolecular interactions between protein chains and solvent. The addition of gums (gaur or xanthan gum) and surfactant (Span20) modified the aqueous hydrocolloid dispersion properties and enhanced capsule formation through electrospraying [71].

**2.2. Inorganic Carriers.** The design of nanoparticles (NPs) and nanoencapsulation systems (considered dimensions of developed nanocarriers are less than 1  $\mu\text{m}$  in the general case and less than 100 nm in the pharmaceutical and cosmetic fields) can significantly increase the surface area to volume ratio of nanosystems. It is reported that nanoscale particles can easily penetrate the cellular walls, thus improving bioavailability of BASs [36]. However, the size of the particles can enhance mucoadhesive ability and susceptibility to enzymatic degradation [36].

TABLE 1: Effect of various parameters on carrier efficiency.

Parameters	Purpose	Carrier material	BASs/BAFAs	Encapsulation effect	Ref
Structural	Composition of materials and auxiliary components	MD GA WPC MD-WPC GA-WPC GA-MD	Blackberry juice <i>Lactobacillus acidophilus</i>	Stabilized bioactive compounds and enhanced viability of <i>L. acidophilus</i>	[38]
Functional	Solubility Viscosity	GA MD	Propolis	Decreased viscosity and enhanced solubility of MD and GA	[39]
Organoleptic	Flavor	Palm oil Camellia oil Gelatin Sodium caseinate	Bitter peptides from wheat gluten	Masked bitterness by forming an intermediate lipid layer which reduces direct contact with taste buds	[40]
Physicochemical	Resistance to temperature	Potato starch	Curcumin	Enhanced thermal stability (180°C, 2 h) compared to unencapsulated curcumin	[41]
Physiological	Release mechanism and rate	Corn starch	Ascorbyl palmitate	Slowed release rate under simulated GIT conditions	[42]

GA: gum Arabic; MD: maltodextrin; WPC: whey protein concentrate.

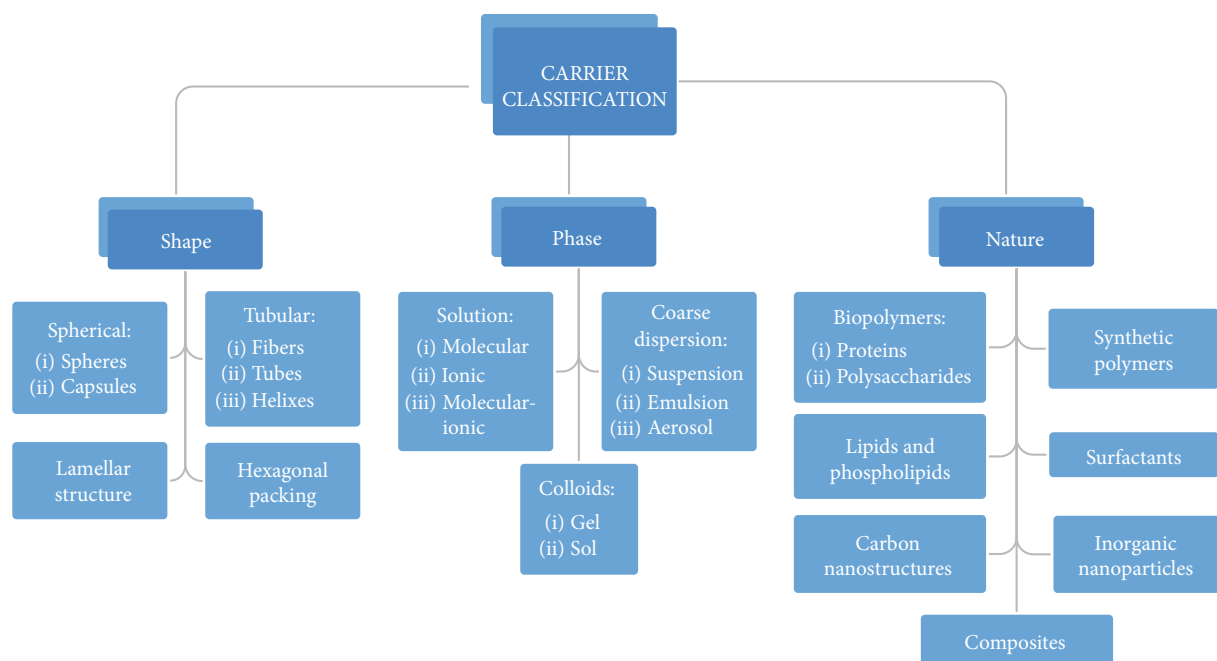


FIGURE 1: The scheme of carrier classifications.

Inorganic NPs as BAS carriers are characterized by easily synthesize, particle size control, high availability, biocompatibility, stability, and efficient affinity with encapsulated biomolecules [80, 81]. The difference in composition, shape, surface morphology, and charge significantly influenced the release mechanism and potential toxicity of nanocarriers (Figure 2) [82].

Inorganic NPs can be divided into several groups: (1) metals/metal oxides (mostly spherical): gold, silver, platinum zinc, aluminum, iron (II, III), or titanium (IV) oxide NPs [83]; (2) silicon oxide (IV) NPs [84]; (3) carbon

(spherical, elliptical, cylindrical, and tubular) [85]; (4) quantum dots [86]; (5) layered double hydroxides (LDHs) which consist of positively charged hydroxide-like layers of metal hydroxide and interlayer regions occupied by anions and water molecules and stabilized by hydrogen bonding [87]. However, encapsulation of BASs into inorganic NPs is currently limited in the food industry. Metal NPs and their complexes are mainly used for drug and biomolecule (proteins and nucleic acids) deliveries to target cells as well as designing antimicrobial films and biosensor [88].

TABLE 2: Carrier-based natural polymer composites.

Carrier material	Addition to carrier material	Carrier formation mechanism	BASs/BAFAs	Encapsulation method	Particle size	Food application	Ref
Chitosan	GA MD	Electrostatic interaction and enzymatic cross-linking	Peppermint oil	Complex coacervation followed by spray drying	10–125 $\mu\text{m}$	Vegan system for potential applications in food	[72]
	GG	Intermolecular hydrogen bond interaction	Astaxanthin	Pickering emulsion	22–48 $\mu\text{m}$	Natural food-grade NPs for designing functional foods	[73]
	TPP	Electrostatic interaction between the phosphate group in TPP and the amino in CS or cross-linking/hydrogen bonds between CS and TPP	Curcumin	Ionic cross-linking	280 nm	Edible coating	[74]
WPI	BC	Hydrophobic interactions or hydrogen bonding	Catechin	Electrospraying	180–240 nm	Design catechin-encapsulated foods with longer shelf life	[17]
	LRA	Reactive sulfhydryl groups (-SH); C-N stretching vibration or N-H bending vibration; hydrogen bonding and hydrophobic interaction	Cholecalciferol	Heat-induced gelation	—	Delivery system of vitamin D3 as an additive in food industry, such as low-fat food, puddings, soft capsules, and fruit drinks	[75]
	Dextran	Conjugates prepared through Maillard-based glycation	<i>Lactobacillus plantarum</i>	Extrusion	7–8 $\mu\text{m}$	Development of functional probiotics	[76]
SA	SPI	Intermolecular hydrogen bonds and/or weak electrostatic attraction between the carboxylic anionic groups on the polysaccharide chain and cationic groups on protein surface	Lycopene	Emulsification (emulsion gel beads)	8 $\mu\text{m}$	Encapsulated food lipid-soluble nutrients	[77]
	CP MD	Electrostatic interactions (maximum binding capacity of $\text{Zn}^{2+}$ is higher than that of $\text{Ca}^{2+}$ because of the former's ability to bond to the OH- and COO- groups of alginate and pectin, while calcium can only interact with COO- groups)	$\alpha$ -tocopherol/ lime oil/ rosemary oil	Ionic gelation followed by spray drying	233–332 nm	Food additives	[78]
	CS	Electrostatic interaction between $\text{Ca}^{2+}$ ions and -COO- group	<i>Moringa oleifera</i> leaf extract	Ionic gelation	80–120 nm	New advanced/intelligent food products	[79]

BC: bacterial cellulose; CP: citrus pectin; CS: chitosan; GA: gum Arabic; GG: guar gum; LRA: lotus root amylopectin; MD: maltodextrin; SA: sodium alginate; SPI: soy protein isolate; TPP: tripolyphosphate.

Inorganic NPs can be a polymer matrix by nanocomposite formation. Nanocomposites are new class of materials, used as biodegradable and edible films [89]. The demerits of these nanocomposites include nonuniform dispersion of NPs through organic system and agglomeration. It is reported that modifying surface of particles may curb the issues and improve their applications [90]. LDHs can form positively charged layers within a three-dimensional grid of silicate layers of nanocomposites that improve the mechanical properties of final materials (Figure 2).

Encapsulation efficiency (EE, %) and loading capability (LC, %) are key quality indices of an encapsulation system.

EE is defined as the ratio of the loaded amount of core material to the total mass of the employed core material, whereas LC is calculated as the loaded mass of core material, divided by the mass of the whole encapsulation system [91]. The EE and LC values vary widely and depend on the type of core materials used, the composition, ratio, and encapsulation method, among others [92, 93].

### 3. BAS Characteristics

Functional food is an emerging market worth over \$267 billion by 2027 [94] in the food industry [1]. Functional food

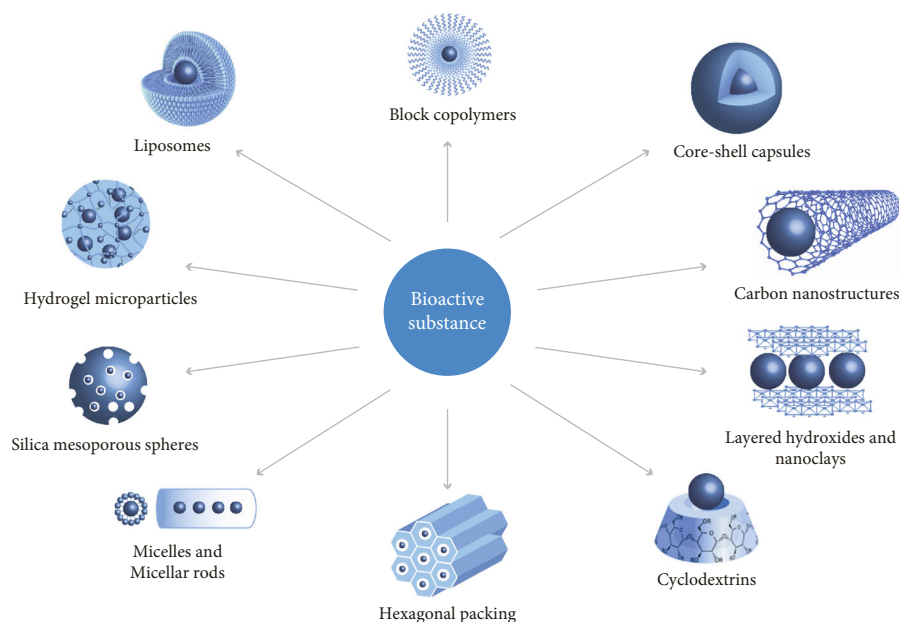


FIGURE 2: Encapsulation of biologically active substances in various types of carriers.

products enriched with bioactive compounds are limited due to their poor bioavailability, solubility, off-flavor, and less stability during processing and storage [1]. Different encapsulation systems have been developed to overcome these drawbacks.

Bioavailability is defined as the fraction of nutraceutical that reaches the systemic circulation and specific sites where it carries out biological functions on the consumer [95]. For example, a zein nanoparticle/oil double epigallocatechin gallate- (EGCG-) loaded Pickering emulsion was prepared [96]. The results showed that the encapsulated system released less EGCG with enhanced bioavailability compared to free-form EGCG. The EE was approximately 52% and remained unaltered for 8 weeks under different storage conditions [96].

Poor water solubility is one of the key characteristics of hydrophobic BASs (e.g. carotenoids, fat-soluble vitamins, polyphenols, and fatty acids) [97, 98]. Encapsulation of these ingredients broadens their application in the food systems. Others have used GA and maltodextrin as wall materials to encapsulate propolis extract by spray drying. The microparticles had high EE (79%) and enhanced antioxidant activity [39]. The authors used maltodextrin and GA due to their high solubility and low viscosity, thus simplifying the spray drying processes. The encapsulation showed good retention of compounds present in the propolis microparticles [39].

Masking off-flavors is an efficient tool for taste modification. Rajanna et al. [99] used pullulan (PUL) during electrospinning of bitter casein-derived peptides for milk fortification. The peptide-loaded nanofibers had a diameter and EE of 100 nm and 86%, respectively. Fourier-transform infrared spectroscopy (FTIR) spectra and X-ray diffraction (XRD) diffractograms showed no interaction between the functional groups of peptides and pullulan, thus retaining their functionality [99].

High stability of BASs in acidic conditions, UV light, temperature, and ionic strength should also be considered when designing encapsulation system. Iqbal et al. [8] utilized modified starch as an emulsifier in O/W nanoemulsions of curcumin and quercetin encapsulation. The results showed that 5 wt% modified starch, and 10 wt% oil formed a stable formulation with 175 nm particle size. Nanoemulsions maximized the solubility of the compounds compared to oil and water. In addition, nanoemulsions loaded with curcumin and quercetin were stable for 5 months under different processing conditions and thus provide an avenue for future application in the food industry [8].

Drosou et al. [11] encapsulated  $\beta$ -carotene dissolved in corn oil to form food-grade nanofibers from pullulan (PUL) and whey protein isolate (WPI) via coaxial electrospinning. The EE of WPI: PUL and PUL nanofibers were 90% and 95%, respectively [11]. According to the kinetic plots of degradation, oxidation of the core substance ( $\beta$ -carotene) was delayed under different storage temperatures, water activity, and UV-Vis irradiation compared to PUL. This intriguing observation was ascribed to the stronger interactions between protein components and  $\beta$ -carotene from being closer to the surface of the nanofiber [11].

#### 4. Encapsulation Methods

Electrospinning [16], electrospraying [17, 18], spray drying [19, 20], microfluidics [21, 22], extrusion, 3D printing [23], coacervation [24], lyophilization [25], incorporation into nanotubes [26], porous micro-/nanospheres [27, 28], nanocomposites [29, 30], isoelectric precipitation [31], antisolvent coprecipitation [32], and ionic gelation [33] are the main encapsulation methods and details (Figure 3 and Table 3) described below. It is important to consider the sensitivity of BASs and processing conditions, as this may influence its functionality (Table 3).

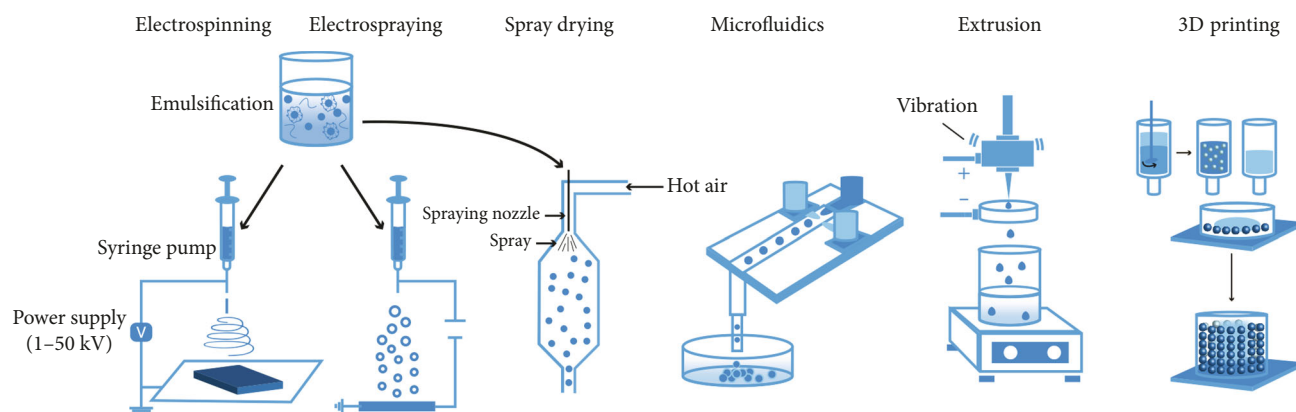


FIGURE 3: Main principles of different encapsulation methods used in the food industry.

**4.1. Electrospinning and Electrospraying.** Electrospinning and electrospraying are single-stage technologies which use high electrostatic potentials of stretching polymer solutions (or polymer melt) into fibers or particles, respectively. These technologies are cost-effective, straightforward with several benefits, including a wide range of reusable spinnable materials, controlled processing conditions, and the ability to produce fibers without high temperature or pressure [100, 101].

A typical electrospinning and electrospraying consists of four components mainly a high voltage source (1-50 kV), syringe pump, spinneret, and a collector in the form of flat plate or rotating drum (Figure 3) [102]. In electrospinning and electrospraying, polymer solutions (or polymer melts) are injected into the capillary spinneret at 0.01–5 mL/h flow rate which forms droplets when exiting the needle nozzle. It is reported that when electric voltage passes through the spinneret and charges the droplet, it leads to the formation of a “Taylor cone” [103]. When the voltage exceeds the critical value at which the repulsive force overcomes the surface tension of the droplet from the end of “Taylor cone,” an electrospun fiber is formed [104]. It is reported that the utilization of higher molecular weight substances can lead to jet formation which is ascribed to efficient entanglement of polymer chains. However, when the concentration of the solution is low, aerosol droplets are formed [104]. The highly charged droplets are deposited on the collector as micro NPs [105]. Electrospinning and electrospraying require no heating system and thus are suitable for encapsulating very sensitive BAFAs (i.e., probiotic bacteria) [106]. The main drawbacks are challenges with upscaling [107] and high fiber diameter distribution in the case of electrospinning [108].

The production of electrospun or electrosprayed particles are dependent on solution properties (i.e., conductivity, viscosity, and surface tension), tool parameters (i.e., applied electric field, solution flow rate, and distance between the needle tip and collector), and environmental conditions (i.e., temperature and humidity). By changing parameters, the size and morphology of encapsulated structures can be altered for specific applications [102]. The direct incorporation of BASS in polymer carrier or randomly distributed in

fibers/particles (cosolubilization of core and wall materials) is commonly practiced during encapsulation. Another strategy is to form a core-shell structure using two capillaries, by inserting the smaller capillary into the larger one. The active component is delivered through the internal capillary spinneret while polymer solution is extruded via an external capillary tube [11]. This approach is multipurpose as the liquid core does not require electroforming.

Paximada et al. [17] applied electrospraying technique to encapsulate catechin in protein-cellulose particles. The EE was 98% with varied particle size between 180 and 240 nm. Further analysis showed that encapsulated catechin was stable and withstood heating, moisture, and dissolution [17]. This study demonstrated that electrospraying can be used to produce edible particles with prolonged shelf life. In addition, Khoshakhlagh et al. [109] designed a nanocapsule from *Alyssum homolocarpum* seed gum (AHSG) to encapsulate D-limonene by electrospraying at 20 kV and 0.1 mL/h flow rate. The addition of AHSG (0.5% w/w) with various concentrations of D-limonene (from 10% to 30% of the gum weight) and 0.1% Tween 20 formed stable smooth capsules [109]. The authors reported that 10 and 20% D-limonene decreased the surface tension and conductivity of the solution. In addition, the nanocapsule morphology was changed to nanofibers at 30% D-limonene O/W emulsion. The particle size ranged between 35 and 90 nm and increased with the increase of D-limonene concentration [109]. The EE and LC of D-limonene nanocapsules for 10%, 20%, and 30% O/W emulsions are listed in Table 3. These experiments showed that electrosprayed AHSG NPs are new and effective carriers for BAFA encapsulation.

Moreno et al. [16] encapsulated phenolic-enriched extracts (PEE) from pulp, seeds, and skin of orange chilito into zein-based matrixes using the electrospinning technique. The addition of zein matrixes increased the thermostability of PEE with high EE (more than 90%, see Table 3). The cross-linking of zein fibers with glutaraldehyde vapors improved the water and morphological stability of carriers. Furthermore, the release of phenolic compounds (rosemary acid, caffeic acid, and its derivatives) was delayed and thus increased the shelf life of their antioxidant properties [16]. This study demonstrated that it is possible to

TABLE 3: Efficiency comparison of BAS/BAFA encapsulation methods.

Encapsulation method	Carrier material	BAS/BAFA	EE (%)	LC (%)	Results	Ref
Electrospraying/ electrospinning	WPI-BC	Catechin	98		High thermostability High stability under moisture	[17]
	WPC (30%)	OLE (0.05%)	84		Improved polyphenol profile of OLE	[18]
		OLE (0.1%)	77			
	WPC (20%)	OLE (0.05%)	71			
		OLE (0.1%)	68			
	SPI	$\alpha$ -Linolenic acid	67		High thermostability Emulsions produced via high-speed homogenization (HSH) were significantly different compared to HSH and ultrasonication	[63]
	WPC		61			
	Gelatin		40		Morphology of capsules changed (irregular shape $\rightarrow$ spherical $\rightarrow$ fibers) with enhanced flavor	[109]
	AHSG	D-limonene (10%)	93	9		
		D-limonene (20%)	87	16		
	Zein	D-limonene (30%)	75	20	High thermostability Cross-linked zein fibers (with glutaraldehyde vapors) had high water stability coupled with slowed release of BASs	[16]
		PEE (from pulp)	94			
		PEE (from skin)	92			
	WPC	Lycopene	75		High thermostability High stability under moisture	[156]
	Dextran		58			
CS		3				
Spray drying	WPC	Lycopene	28		Temperature influenced the stability of BASs Poor encapsulation efficiency	[156]
	Dextran		16			
	CS		1			
	Rice protein	Propolis extract	90		Preserved antioxidant activity High thermostability (for particles produced with pea and soy proteins) Low hygroscopicity	[19]
	Pea protein		89			
	Ovalbumin		73			
	Soy protein		70			
	GA-XG (0% PJ)	Pomegranate seed oil	93	14	High thermostability Improved oxidative stability of oil PJ increased EE PJ increased phenolics and influenced powder color	[20]
	GA-XG (50% PJ)		94	14		
	GA-XG (100% PJ)		97	14		
Coacervation	SPI-CS	Algal oil	96		High oxidative stability Low polydispersity	[118]
	SPI-CS (with transglutaminase)		97			
	WPC-PE	D-limonene	88		WPC : PE = 4 : 1 had high L* index (color value)	[24]
	Casein-GT	$\beta$ -Carotene	79		Increased antioxidant activity High physical stability	[69]
	Casein	Vitamin B <sub>9</sub>	40	31	Lysine or arginine prevented aggregation of particles in an aqueous environment High oral bioavailability	[157]
Lyophilization	WPI-MD-SA (0% MD)	Flaxseed oil	27		Enhanced oxidation of the oil	[62]
	WPI-MD-SA (10% MD)		64			
	WPI-MD-SA (20% MD)		95		Improved water solubility High antioxidant activity	[25]
	MD	Catechin NE (10% w/w MD)	77			

TABLE 3: Continued.

Encapsulation method	Carrier material	BAS/BAFA	EE (%)	LC (%)	Results	Ref
	GA	Catechin NE (10% w/w GA)	82			
	MD-GA	Catechin NE (10% w/w MD-GA)	81			
	SPI	<i>Lactobacillus acidophilus</i>	95		Improved survival and viability in gastrointestinal conditions	[120]
	SA		92			
	I-CG		88			
	Starch		79			
	PCL	Chlorophyll	58		High photostability	[122]
	Liposomes	Vitamin D <sub>3</sub>	88			
	Liposomes-CS (0.01% w/v CS)		98		Improved aggregation stability and mucoadhesiveness (for polymer-lipid hybrid particles)	[22]
	Liposomes	Vitamin K <sub>2</sub>	94			
Microfluidics	Liposomes-CS (0.005% w/v CS)		98			
	W/O/W emulsion	Elderberry extract Norbixin	55 75		High color retention	[21]
	O/W emulsion-protein (gelatin : casein = 1 : 1)	Fish oil			High oxidative stability	[126]
	SA	<i>Lactobacillus acidophilus</i> LA3			Stabilized under storage conditions Improved survival and viability in gastrointestinal conditions	[134]
	SA-shellac					
	WPC (10%)	<i>Bifidobacterium longum</i> BL-05	85			
	WPC (7.5%) + PE (0.5%)		89		Increased storage stability Improved survival and viability in gastrointestinal conditions	[135]
Extrusion (3D printing)	WPC (5%) + PE (1%) PE (2%)		93 95			
	W/O/W emulsion-SA	<i>Bifidobacterium lactis</i> BB-12			Stabilized under storage conditions Improved survival and viability in gastrointestinal conditions	[136]
	SA	C-Phycocyanin			High thermostability	[129]
	SA	Microalga <i>Arthrospira platensis</i>			Improved color stability Maintained antioxidant activity	[23]
	MWCNTs (with peptide linkers)	Vitamin B <sub>9</sub>			Enhanced resistance to enzymatic degradation	[85]
		Lycopene (1 mg/mL)		5	High thermostability	
		Lycopene (0.8 mg/mL)		5	High photostability	
Introduction into nanotubes	$\alpha$ -LA	Lycopene (0.6 mg/mL)		2	Released lycopene under low pH condition Improved antioxidant activity Improved colloidal stability	[26]
		Caffeine (caffeine : $\alpha$ -LA = 1.5 : 20)	97	9		
	$\alpha$ -LA	Caffeine (caffeine : $\alpha$ -LA = 2 : 20)	97	12	Improved physical stability	[142]



TABLE 3: Continued.

Encapsulation method	Carrier material	BAS/BAFA	EE (%)	LC (%)	Results	Ref	
Introduction into porous micro-/nanospheres	MSNs-fucoidan	Curcumin (0.25 mg)	≈100	6	Improved water solubility Improved release rate (>80% within 24 h)	[28]	
		Curcumin (0.50 mg)	93	9			
	MSNs	Curcumin (0.25 mg)	89	5	Enhanced antitumor activity		
		Curcumin (0.50 mg)	81	9			
	MSNs-PLA	CEO			Sustained cumulative release profile Effective against <i>S. aureus</i> and <i>E. coli</i>	[27]	
Development of nanocomposite materials	ZnFe-LDHs	Vitamin C			Improved stability	[145]	
	MgFe-LDHs						
		Benzoate		24	Efficient antimicrobial activity Slowed release kinetics	[29]	
	Zn-Al LDHs	2-Chloro-5-nitrobenzoate p-Hydroxybenzoate		40 42			
		MMT-CS	Rosemary EO			Improved antimicrobial property Improved solubility and tensile strength	[158])
		SA-clay	Marjoram EO Cinnamon EO clove EO			Improved antimicrobial activity Marjoram EO had a higher antimicrobial effect	[159]
	MMT HNT	Thyme oil/orange oil Thyme oil/orange oil			Modulated aroma release	[30]	
Isoelectric precipitation	Chickpea protein	Curcumin	79	9	High thermostability High photostability	[149]	
	Krill protein	(oil : protein = 20 : 80)	Krill oil	24	8	Reduced LC and EE Krill oil/krill protein ratio influenced surface structure	[31]
			(oil : protein = 40 : 60)	14	6		
		(oil : protein = 60 : 40)	10	5	Lipid classes and fatty acid composition were not influenced		
Antisolvent coprecipitation	Zein-lecithin (zein : lecithin = 1 : 1)	Curcumin	≈100	5	High thermostability High photostability	[67]	
	Zein		42	4			
	Lecithin		87	9	Improved solubility		
	Gliadin	Curcumin	44	3			
	Lecithin		71	5			
Stepwise antisolvent precipitation	Gliadin/lecithin		91	6	High thermostability High photostability	[32]	
	Gliadin/lecithin		87	6			
	Lecithin/gliadin		77	5			
Ionic gelation	GA-CS (GA : CS = 1 : 1)	Saffron extract (5 mg/mL)	29		High thermostability High photostability	[33]	
	GA-CS (GA : CS = 1 : 2)		Saffron extract (10 mg/mL)	52			

Carrier materials: AHSG: Alyssum homolocarpum seed gum; BC: bacterial cellulose; CS: chitosan; GA: gum Arabic; Gli: gliadin; GT: gum tragacanth; HNT: halloysite (clay); I-CG: iota-carrageenan; LDHs: layered double hydroxides; MD: maltodextrin; MMT: montmorillonite (clay); MSNs: mesoporous silica NPs; MWCNTs: multiwalled carbon nanotubes; PE: pectin; PLA: poly(lactic) acid; PLC: polycaprolactone; SA: sodium alginate; SPI: soy protein isolate; TP: tremella polysaccharide; WPC: whey protein concentrate; WPI: whey protein isolate; XG: xanthan gum;  $\alpha$ -LA:  $\alpha$ -lactalbumin. BAS/BAFA: CEO: clove essential oil; EO: essential oil; OLE: olive leaf extract; PFAs: polyunsaturated fatty acids; PEE: phenolic-enriched extracts; PJ: pomegranate juice; NE: nanoemulsion.

develop bioactive coating structures based on zein fibers containing chito PEE as a promising packaging material for hydrophilic or lipophilic food ingredients.

Soleimanifar et al. [18] prepared NPs containing olive leaf extract (OLE) from whey protein concentrate (WPC)

via electrospraying. The sizes of the spherical NPs (mean size = ~232.3 to 659.8 nm) depended on the concentration of applied WPC and OLE. The increase in concentration of OLE and WPC enhanced the EE (%). High performance liquid chromatography (HPLC) analysis showed that

nanocarriers from 15% WPC with 500 ppm phenolics had the highest concentrations of oleuropein, tyrosol, and caffeic acid. In contrast, carriers from 15% WPC and 1000 ppm phenolics presented the highest level of hydroxytyrosol [18]. This study further demonstrated that sensitive OLE can be encapsulated and used to design functional food and nanodelivery of pharmaceuticals. In the study of Fareed et al. [110], *Lactobacillus acidophilus*, a probiotic, was encapsulated in blended nanofibers of GA and polyvinyl alcohol using an electrospinning technique. The results showed that probiotic-encapsulated nanofibers had high average size, zeta potential, moisture contents, thickness, tensile strength, and elongation at break compared to the free probiotics. *In vitro* assay showed that encapsulated probiotics had a significantly high viability rate compared to free cells, which lost their viability under simulated gastrointestinal conditions [110]. The addition of starch/water soluble yellow mustard mucilage to electrosprayed nanocapsules loaded with thymol and carvacrol improved EE (84.10%), surface morphology, and release kinetics [111].

**4.2. Spray Drying.** Spray drying is a method of producing microparticle core-shell by rapid drying of dispersed substance under hot gas flow to disperse medium into insoluble shells [112]. In the nozzle of a spray dryer, the liquid flow disintegrates into small droplets which transit into a solid state due to rapid evaporation of the dispersed medium. It is reported that the significant increase in surface area led to intense mass and heat exchange between hot dry gas jets and droplets. Nowadays, spray drying is one of the commonly used methods of drying and microencapsulation of lipophilic compounds in the food industry [113].

The microencapsulation of propolis extracted from rice, pea, soy, and ovalbumin proteins as wall materials through spray drying followed by *in vitro* digestion analysis of the obtained microcapsules was reported [19]. Propolis is flavonoid-enriched material that confers health benefits to consumers. However, the utilization of propolis in the food sector is limited due to its undesirable aroma and poor solubility in water. Thus, microencapsulation masked the undesirable aroma, enhanced antioxidant activity, and EE (90.20%). The *in vitro* digestive system showed that pea protein-loaded microparticles with Minas frescal cheese had the best-controlled release profile compared to other proteins. Furthermore, rice protein-loaded microparticles were suitable for pudding fortification due to an excellent release of phenolic compounds (i.e., 100%) [19].

Yekdane and Goli [20] screened the properties and oxidative stability of pomegranate seed oil (PSO) microcapsules made from GA, xanthan gum enriched with pomegranate juice (PJ). Different concentrations (i.e., 0%, 25%, 50%, 75%, and 100%) of PJ were introduced into the solution of the capsule material before being spray-dried. The addition of 100% PJ increased EE (96.3%) of microcapsules with an intact and quite smooth surface. The experiment demonstrated that the encapsulation with pomegranate juice enhanced the oxidative stability of PSO [20]. Others have recently speculated that the addition of water-soluble yellow mustard mucilage enhanced the emulsion stability, EE

(91%), and the release pattern ( $R^2 = 0.991$ ) of the essential oils, thymol and carvacrol, and polyphenols [114].

**4.3. Coacervation.** Coacervation is a method of producing polymer droplets from the solution of a high-molecular compound (HMC), when conditions (i.e., temperature and composition) change [115]. Coacervation enables the transition from unrestricted mutual solubility of liquids, mixed freely, to a restricted mutual solubility. This system is divided into two layers: the layer of equilibrium liquid with a low content of HMC and the layer with a high concentration of HMC also called coacervate. Coacervation occurs in two- and multi-component solutions of organic and inorganic compounds. However, aqueous solutions of proteins and polysaccharides are the most studied [116]. There are simple and complex coacervations. Simple coacervation is the interaction of the dissolved film-forming polymer with a low-molecular-weight nonsolvent (i.e., gelatin with ethanol or sodium sulfate). The simple coacervation method is used to microencapsulate oils, oil solutions, and water-insoluble BASs. On the other hand, complex coacervation involves the interaction of two polymers whose macromolecules are oppositely charged (i.e., aqueous solutions of gelatin and GA, acetone solutions of cellulose ethers, and polysiloxane) [115].

In microencapsulation of BASs via complex coacervation, two high-molecular-weight compounds interact with each other, thus one film-forming polymer, and the second is a precipitating polymer. Hydrophobic BASs are dispersed in an oil solution which is emulsified in a film-forming polymer solution. A high-molecular-weight nonsolvent is added to the emulsion, and pH adjusted (below isoelectric point) to charge the opposite polymers. Finally, the pair of macrocation and macroanion are attracted to each other and form the shell of the microcapsule [116, 117].

Yuan et al. [118] investigated the complex coacervation of soy protein isolate (SPI) with chitosan (CS) and algal oil. The results showed that the optimal complexation pH and CS/SPI ratio were 6.0 and 0.125 g/g, respectively. The rheological and microstructure analyses showed that SPI-CS coacervates had a viscoelastic solid behavior with a highly interconnected gel-like network structure [118]. The SPI-CS coacervate showed an increased EE (95.94%) with improved oxidative stability compared to the SPI-encapsulated microcapsule. Further transglutaminase of cross-linking enhanced the EE (97.36%) with lower lipid hydroperoxides and hexanal values [118].

Ghasemi et al. [24] encapsulated D-limonene in whey protein concentrate- (WPC-) pectin nanocomplexes. The results showed that nanocomplex fabrication of mixing 4% w/w WPC, 1% w/w low methoxyl pectin, and 50% w/w maltodextrin solutions at pH 3 had the least stability (83%), higher viscosity (35 mPa·s), and brightness ( $L^*$  index = 75.14) [24]. Atomic force microscopy revealed spherical NPs of WPC-pectin nanocomplexes with average size of 100 nm. The highest EE was 88% at pH 3. Finally, the optimum WPC/pectin nanocomplex (the ratio is 4:1) loaded with D-limonene may be used in the food industry to shield flavor active compounds during processing and storage with controlled release [24].

**4.4. Lyophilization/Freeze Drying.** Lyophilization is a soft drying technique of thermolabile substances (i.e., probiotics, fatty oils, and flavonoids). These thermolabile BASs are usually frozen, and the solvent is sublimated in a specialized vacuum unit before drying [119]. The advantages of lyophilization include low-temperature treatment and preservation of the dispersed phase, the structural integrity is maintained, and the biological activity of BASs is not altered.

Fioramonti et al. [62] lyophilized flaxseed oil microcapsules with maltodextrin (MD) at various concentrations (0, 10, and 20% w/w). The multilayer emulsions with interfacial layer were obtained by electrostatic precipitation of sodium alginate on oil droplets coated with whey protein isolate at pH 5. MD was added and exposed to freeze drying (-20°C) for 3 days at 40 Pa [62]. The results showed that sonication coupled with freeze drying significantly enhanced the oxidation of the oil. The addition of 20% MD to the emulsion increased the EE (95.44%). Also, an increase in the concentration of MD enhanced the water activity of microcapsules from 0.14 to 0.33 [62]. Others have also reported that an increase in wall materials improved the hygroscopicity and water solubility (92%) of catechin nanoemulsion [25]. In addition, catechin nanoemulsion which contained GA and mixture of GA and MD had high EE and flavonoid recovery values compared to MD alone. Furthermore, MD and mixture of GA and MD samples exhibited higher antioxidant activity compared to GA-treated samples [25]. The findings of the study may be applied to develop effective ingredients for functional foods or beverages.

*Lactobacillus acidophilus* encapsulated through lyophilization using various wall materials such as SPI, sodium alginate (SA), iota-carrageenan (I-CG), and starch was recently reported [120]. The EE of SPI (95%) and SA (92%) microbeads were higher compared to I-CG (88%) and starch (79%). Also, SPI and SA microbeads showed better survival rate compared to I-CG and starch ones. These findings suggest that SPI and SA are feasible materials for the microencapsulation of probiotics with improved viability under simulated gastrointestinal conditions and in food matrices.

**4.5. Microfluidics.** Over the last two decades, microfluidic techniques have attracted great interest and grown exponentially in various fields, particularly in food science for the encapsulation of ingredients. An essential characteristic of microfluidic systems is the use of tiniest concentrations (up to  $10^{-18}$  L) of fluids moving in a laminar flow within channels with dimensions ranging from tens to hundreds of microns (Figure 3) [121]. Microfluidic technology enables the repetitive fabrication of micron-size particles in a narrow size distribution and uniform shape. A common drawback of microfluidic technique is the inability to accurately control over processing variables; meaning one parameter cannot be changed independently over the other. However, various microfluidic strategies such as droplet microfluidics [122, 123], continuous flow thin film microfluidic [124], and rapid mixing microfluidic [125] enable control over the process parameters of the encapsulated particles, enhance stability and solubility of bioactive compound, and improve shelf life of functional foods.

Droplet microfluidics was used to formulate spherical polycaprolactone particles loaded with chlorophyll of 68 to 247  $\mu\text{m}$  size. Encapsulation enhanced chlorophyll stability and thus harness its food applications [122]. Nanoliposomes encapsulated with vitamin D<sub>3</sub> and K<sub>2</sub> were successfully designed via semicontinuous microfluidic technique. The addition of chitosan enhanced the mucoadhesiveness and stability of designed liposomal structures and thus may be used to develop nutraceuticals [22]. Others have encapsulated natural pigments [21] and fish oil [126], using microfluidic. Norbixin and anthocyanins encapsulated W/O (palm oil)/W emulsions with particle sizes 180  $\mu\text{m}$  and 190  $\mu\text{m}$  and EE 60% and 50%, respectively, were reported [124]. In addition, the particle sizes of fish oil in casein, gelatin, and hydrolyzed whey protein O/W emulsions ranged between 80 and 100  $\mu\text{m}$ . The authors claimed that the thin film vortex fluidic device (VFD) simplified W/O/W emulsions of fish oil to a one-step process without undesirable organic solvents inappropriate in food production, thus saving time and money [124]. A scale-up of microfluidic approaches can enhance high-throughput encapsulation of chemically diverse active ingredients [127].

**4.6. Extrusion and 3D Food Printing.** Extrusion is a direct and convenient method used to encapsulate biologically active compounds with the aim to extend shelf life [128, 129], controlled release [130–132], protective effect [133] of active ingredient in the food industry. Extrusion does not require organic solvents or high temperatures thus safe and suitable for encapsulating thermolabile biologically active compounds. This technique entails mixing the core component with a carrier, extruding the mixture through a nozzle and collecting droplets in a solidification bath, forming matrix-type particles (Figure 3). To improve the preservation of BASs, coextrusion method is preferred for the production of reservoir-type particles through coaxial nozzles [134]. A comparison of extrusion and coextrusion showed that *Lactobacillus acidophilus* LA3 encapsulated via the latter method using alginate was 17% viable after 60 days of storage compared to the former [134]. Beside alginate, extrusion using whey protein concentrate and pectin was proposed as a novel technology of encapsulating BASs and probiotics against harsh gastrointestinal conditions [135]. Additionally, extruded *Bifidobacterium lactis* had a higher (98.5%) survival rate and *in vitro* gastrointestinal simulation (up to 86.1%) in various pH conditions [136]. Others have reported that extrusion enhanced the stability and shelf life of C-phycoerythrin colorant compared to the free form (unencapsulated) [129]. Therefore, extrusion technology provides high encapsulation throughput for delicate and valuable BASs. Others have documented that coupling vibrating equipment with the extrusion process helped achieve a uniform droplet size (Figure 3) [128, 134, 137]. Dripping-extrusion method of encapsulation retained more hibiscus anthocyanin (48%) and color stability ( $\Delta E = 1.42$ ) of yogurt during storage compared to the free extract [128]. Encapsulation parameters are essential as they influenced microparticle characteristics and the effectiveness of

protecting bioactive compounds from environmental and gastrointestinal conditions [137].

The optimum consumer preference of processed foods may be deciphered by understanding flavor perception in different encapsulation structures. Melt extrusion and fluidized bed drying encapsulated flavors in long chewable products obtained increased the flavor perception for an extended period. The authors further mentioned that various encapsulation techniques can be coupled to design desirable food products based on the intended purpose [132].

In recent years, 3D food printing technology has successfully been introduced in the food industry. The principles of the 3D printing technique involve a system based on gelatin, agar, and alginate. These, with other physical or chemical cross-linkers, undergo a liquid-solid transition and become hydrogels with the desired shape during printing (Figure 3). Cookies enriched with extract of microalga *Arthrospira platensis* were recently produced via 3D printing [23]. The encapsulated extract in alginate microbeads was stable under light, heat, and oxygen during baking with an extended shelf life compared to the free form [23].

3D printing of artificial plant tissues may open exciting possibilities to design a novel combination of aromas and textures with great potential in personalized food products. Others have encapsulated live plant cells in pectin gels and printed 3D objects ( $5 \times 10^6$  cells/mL) with precision and reproducibility. 3D food printing had no effects on cell viability and thus kept its functionality [138].

Enzyme encapsulation in hydrogels is of great interest as a reusable system in biocatalysis or analytical applications. Functional biological compositions can be implemented in microreactors, microfluidic devices, biosensors, or in the form of spheres for various applications. For these and other purposes, the transition to 3D structures may provide new opportunities in the food industry [139]. To be precise, the interaction of biomolecules encapsulated in a hydrogel with the surrounding liquid phase is a serious concern to consider when it comes to leaching of undesirable compounds, release control, and other molecule penetration. The combination of 3D bioprinting and automated high-throughput screening of  $\beta$ -galactosidase encapsulated in hydrogels based on poly(ethylene glycol) diacrylate using a mold and fill printing procedure was reported [140]. Therefore, 3D printing technology could be a promising alternative to encapsulate bioactive substances for designing functional foods.

**4.7. Introduction of BASs into Nanotubes.** Carbon nanotubes (CNTs) are nanoscale hollow tubular structures of carbon atoms, formed by rolling graphene sheet into a tube-like structure (Figure 2). CNTs are classified into single-walled carbon nanotubes (SWCNTs) and multiwalled carbon nanotubes (MWCNTs). The outer diameter of the tubes ranged between 0.4 and 2 nm for SWCNTs and 2 to 100 nm for MWCNTs [141]. Fraczyk et al. [85] encapsulated folic acid in multiwalled CNTs through peptide linkers. It was reported that the conjugated folic acid linked to MWCNTs was not toxic to cellular function and resisted proteolytic degradation for up to 7 days [85]. Others have documented the stability and functionality of caffeine nanotubes derived

from  $\alpha$ -lactalbumin ( $\alpha$ -LA) [142]. Partial enzymatic hydrolysis of  $\alpha$ -LA in the presence of a divalent ion produced edible nanotubes with a high potential in the food and cosmetic industries. The results showed that EE of caffeine reached 96.96% and loading capacity 9.21% for the 1.5/20 (w/w) ratio of caffeine/ $\alpha$ -LA. Also, the increase in the ratio of caffeine/ $\alpha$ -La (2/20 w/w) elevated the EE (97.16%) and LC (12.30%). It was estimated that more than 50% of caffeine encapsulated in  $\alpha$ -LA nanotubes remained encapsulated at 8°C and pH 7.5 in the presence of 75  $\mu$ g/mL EDTA [142]. Recently, Chang et al. [26] developed food-sourced protein nanotubes by self-assembly of partially hydrolyzed  $\alpha$ -lactalbumin for lycopene encapsulation. The  $\alpha$ -La nanotubes were characterized by 20 nm in diameter and 200–1000 nm in length. The encapsulated lycopene was stable under different temperature and UV light compared to unencapsulated ones [26]. During transition via gastrointestinal conditions, the nanotubes biotransform to nanospheres with a controlled release of lycopene to the target cell. The colloidal stability and antioxidant activity of the loaded lycopene were enhanced, and thus, lycopene-loaded  $\alpha$ -La nanotubes can be incorporated into the dairy or other sorts of drinks [26].

**4.8. Introduction of BAS into Porous Micro-/Nanospheres.** Properties such as large surface area, ability to change pore diameters (from 2 to 50 nm), versatility (able to encapsulate both hydrophilic and lipophilic compounds), highly biocompatible, precise controlled release in the intestinal pH, and high thermal and chemical stability make mesoporous silica NPs (MSNs) (Figure 2) ideal candidates for encapsulating very sensitive BASs [141].

A complex NP containing disulfide bonds as a curcumin carrier using fucoidan and MSNs as the polymer matrix was designed. Scanning electron microscopy (SEM), transmission electron microscopy (TEM), dynamic light scattering, FTIR,  $N_2$  adsorption, and desorption test showed that the mass ratio of MSNs to fucoidan was 2:1, with the smallest nanosphere particle size ( $295.6 \pm 1.0$  nm,  $-35.2 \pm 0.8$  mV). The EE and cumulative release rate were 90 and 80%, respectively, over 24 h [143]. This study further demonstrated that NPs are a promising composite for delivering BASs. Lu et al. [27] reported immobilized MSNs/clove essential oil incorporated into poly(lactic acid) films. The increase in MSN content in MSN/clove essential oil/poly(lactic acid) improved tensile strength, module, glass transition temperature, and antimicrobial activity of the nanocomposite. The results indicated that the nanoencapsulation system of clove essential oil immobilized in MSNs incorporated in poly(lactic acid) matrix could potentially be used to design active food packaging materials [27].

**4.9. Development of Nanocomposite Materials.** Nanocomposite materials exhibit functionalities that make them ideal in the food industry. Some of these functionalities include a unique structure of layered nanoclay that makes it possible to incorporate biomolecules into interlayer spaces (Figure 2) without altering the chemical and functional properties. Secondly, nanoclays can easily penetrate cells with precise

controlled release of BASs. Lastly, they are less toxic (in some cases, not toxic at all) materials.

Nanoclays had attracted the attention of the packaging industry due to low cost (affordability) and easier to fabricate. Montmorillonite (MMT) and halloysite (HNT) are widely used natural clays to design polymer-clay nanocomposites. The choice of HNT (tubular shape), MMT (platelet-like) clays, nanofiller shape, and their morphology influenced the properties of the crafted nanocomposites [144].

Gasser [145] loaded ascorbic acid (vitamin C) into the interlayer space of layered double hydroxides (ZnFe-LDHs and MgFe-LDHs) also called anionic clay using the anion-exchange method (Figure 2). It was reported that the fabrication stabilized the vitamin C and preserved its biological activity. In addition, the release of the interlayer content (vitamin C) was achieved without altering the functionality due to the ion-exchange reaction or dissolution of the LDH framework [145]. Further study showed the potential applications of cationic and anionic layered nanoclays as nanocarriers for vitamins, antioxidant, and linoleic acid in the food industry [146].

Mishra et al. [29] have developed an antibacterial composite material by encapsulating benzoate and its two derivatives (para-hydroxybenzoic acid and 2-chloro-5-nitrobenzoic acid) between the interlayer distance of Zn-Al LDH. The nanocomposites demonstrated potent bactericidal effects against Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli* strains [29]. The study proved the feasibility of using composites as active antimicrobial materials.

Others have reported that a multilayer film reservoir loaded with clay (MMT or HNT)/essential oil (orange or thyme) had higher adsorption, better interactions with thyme oil, and continuous aroma release compared to HNT. Thus, polymer-clay nanocomposites can be used as aroma-controlled release systems in the food and pharmaceutical (drugs) applications [30].

**4.10. Isoelectric Solubilization/Precipitation.** Isoelectric point (pI) is the pH of a solution at which the net charge of protein becomes zero. Likewise, isoelectric precipitation of protein is the process that leads to precipitate formation due to the decrease of hydration level and repulsive electrostatic force [147]. It is reported that the protein molecules trap BASs present in the medium [148].

Shi et al. [31] reported the feasibility of krill protein isolated with isoelectric solubilization/precipitation as wall material to encapsulate krill oil via freeze drying. Although the capacity of loading oil into microcapsules increased, the EE and LC decreased. Ariyaratna and Karunaratne [149] encapsulated curcumin into a chickpea (*Cicer arietinum*) protein matrix by isoelectric precipitation. The results showed that protein coating protected curcumin by more than 40% at 50°C and 25% at 25°C and 37°C. In addition, the release of curcumin from protein matrix was slower at pH 4 but reached ~100% (pH 2). Lastly, the protein matrix decreased curcumin photodegradation by 60%. Thus, chickpea protein capsules can be used as a protective coating for curcumin in the food industry and as a slow-release carrier in the pharmaceutical industry [149].

**4.11. Antisolvent Precipitation and Coprecipitation.** Antisolvent coprecipitation is a promising technique of encapsulating polysaccharide- and/or protein-based NPs. This is a cheap process that does not require special-purpose equipment [150]. The bioactive compound to encapsulate is dissolved in a binary solvent (usually water and an organic solvent). Different solvent is added to reduce the solubility of bioactive compound and thus supersaturate and precipitate forming NPs [143]. Others have designed ultrafine particles with controlled size distribution using devices such as impinging jet, T-mixer, static mixer, and multi-inlet vortex mixer. However, particle agglomeration may occur due to insufficient repulsion after formation. It was speculated that utilization of ultrasound and the devices mentioned above curbed particle agglomeration [151, 152].

Dai et al. [67] designed zein-lecithin NPs loaded with curcumin by antisolvent coprecipitation with 99.83% EE. FTIR analysis showed that hydrogen bonding and electrostatic and hydrophobic attractions bonded zein, lecithin, and curcumin together. In addition, the bioactive component in zein-lecithin NP composite was stable under heat treatment, UV irradiation, and high ionic strength compared to single zein and lecithin NPs. Therefore, composite zein-lecithin NPs can be used as a delivery system for water-insoluble bioactive compounds with high EE and chemical stability [67].

Yang et al. [32] fabricated curcumin-loaded NPs with gliadin and lecithin via antisolvent precipitation. High EE, low turbidity, improved delivery efficiency with smaller particle size were achieved via antisolvent precipitation compared to stepwise antisolvent precipitation. In addition, antisolvent coprecipitation gliadin-lecithin-curcumin NPs had smoother surface, resistance against light and temperature compared to stepwise antisolvent precipitation of NPs [32].

**4.12. Ionic/Ionotropic Gelation.** Ionic/ionotropic gelation is an effective technique of synthesizing NPs or hydrogel microparticle (Figure 2) by the electrostatic cross-linking of hydrophilic polymeric chains in the presence of hydrophobic ions. The anions combine with the polyvalent cations and thus induce gelation by binding mainly to the anion blocks [153]. It is reported that the utilization of hydrogel beads as carriers enhanced the bioavailability of BASs with sustained controlled release of bioactive compounds [154]. Chitosan NPs prepared by ionotropic gelation technique are widely used for drug delivery. Despite many studies on chitosan NPs, the lack of reproducibility due to varied formulation parameters coupled with a poor understanding of its formation has hindered their potential applications [155]. Nevertheless, Rajabi et al. [33] encapsulated saffron extract into GA-chitosan nanocomplexes by ion-gelation. FTIR and XRD confirmed the bond formation between functional groups (-COO<sup>-</sup> and -NH<sub>3</sub><sup>+</sup>) of two biopolymers and the amorphous structure. TEM analysis showed that the nanocomplexes are spherical, smooth shapes with uniform particle size distribution. In addition, the ratio of CS, GA, and saffron extract significantly influenced the functional properties of nanocomplexes and EE due to increased

attraction between positive and negative biopolymer groups [33]. The release rate of saffron bioactive component—picrocrocin (more than 80% for 60 min) was higher in acidic condition compared to neutral (70% after 4 h) partly due to the presence of high CS in acidic solution. Thus, nanocomplexes can be used as effective carriers to preserve biologically active compounds of saffron for safe delivery via the gastrointestinal tract [33]. Also, Algharib et al. [155] synthesized chitosan NPs with mean particle size and zeta potential of  $67.60 \pm 0.11$  nm and  $+33.23 \pm 1.20$ , respectively. Further analyses showed that the NPs had spherical shapes with good particle size distributions. The identified control parameters forge the path to widen the potentials of chitosan NPs in future food and pharmaceutical applications.

## 5. Biosafety and Bioavailability

The aim of food biosafety is to analyze and eliminate/manage risks that may have adverse effects on human health and the environment. Some carrier materials used in encapsulation systems might be unsafe/toxic; thus, biocompatible materials that integrate into host (human) without injurious effects should be used. It is reported that carrier materials are unsafe if they [46]

- (i) interfere in digestion and absorption processes
- (ii) are cyto- or genotoxic
- (iii) contaminate food products (including transfer from packaging materials).

Sonin et al. [160] reported that the potential cytotoxicity of an encapsulated nanoparticle is dependent on size, shape, surface area, and attraction between opposite charges.

Polysaccharide-based particles obtained by covalent/ionic cross-linking, polyelectrolyte complexation, or self-assembled with hydrophobic molecules showed null toxicity like natural-based biopolymers. However, their safety can only be guaranteed if the residues of unreacted covalent cross-linkers posed no effects on humans [161]. It is worth mentioning that some solvents used are toxic. Thus, the utilization of Food and Drug Administration (FDA) approved generally recognized as safe solvents can assure the biosafety of polysaccharide-based materials.

It is reported that some inorganic NPs are insoluble in the gastrointestinal tract (e.g., titanium dioxide and silicon dioxide), while others are partially or completely soluble (e.g., silver oxide and zinc) [82, 162]. Partially/completely soluble NPs can stimulate the overproduction of reactive oxygen species (ROS) and thus induce oxidative stress leading to an imbalance physiological redox-regulated functions, DNA damage, and cell death via apoptosis [81]. Others have documented that anionic clay is rapidly excreted from the body and does not accumulate in organs, whereas silicon NPs are biodegradable and excreted as orthosilicic acid [163, 164]. Nanoclays are biocompatible and had low or null toxicity and thus may be used as mineral supplements [165]. *In vivo* analysis with Wistar rats using low-molecular-weight chitosan (1–4 mg/kg) showed low cytotoxicity. In addition,

intravenous administration had no side effects on the systemic hemodynamics [160].

Oral administration of carbon NPs with mice at various concentrations showed no effects on reproductive health, hormonal levels, and sperm quality [166, 167]. On the other hand, chicken embryo exposed to carbon NPs at 50, 500, and 5000  $\mu\text{g}/\text{mL}$  showed a dose-dependent decrease in survival rate [168]. Furthermore, an increase in intracellular vacuoles, severe cell membrane, and mitochondrial damage was observed [168]. Others have documented that high dose (50 mg/kg/day) of single-walled carbon nanotubes significantly ( $p < 0.05$ ) decreased sperm count, viability, and motility and increased oxidative stress compared to multiwalled carbon nanotubes [169]. Intravenous administration of nanoscale NPs ( $\sim 2000 \mu\text{g}/\text{mL}$ ) to mice showed evidence of DNA fragmentations, and chromosomal aberrations of the spermatozoa. In addition, the pregnant functionality of the female mice decreased significantly compared to control [170]. The observed contradiction with regards to biosafety of nanomaterials used as wall material for encapsulation of BASs raises serious concern and thus calls for a robust, high-throughput standardization of biomaterial safety. The Center for Food Safety and Applied Nutrition is currently researching some approaches of determining biomaterial toxicity. The potential toxicity of biomaterials for encapsulation may be minimized or curbed by using FDA-approved nanomaterials.

The term bioavailability means the concentration of encapsulated BASs absorbed and transported into the bloodstream to elicit physiochemical processes [171]. The release of BASs during digestion to be absorbed in the small intestine is termed bioaccessibility [171, 172]. It is reported that shape, form, and wall material can significantly influence the bioavailability of encapsulated BASs [172]. Peng et al. [173] demonstrated that encapsulated curcumin NPs were highly (2.7–3.6-fold) bioavailable compared to the free (control) curcumin. In addition, gastric acids triggered the transformation of the control NPs (88.3%) compared to the encapsulated curcumin (48%) and thus had significantly lower bioaccessible (9.1%) curcumin [173]. Similarly, *in vitro* simulated poultry GIT conditions demonstrated that encapsulation enhanced the release of enzymes from alginate NPs with concomitant good bioavailability of phosphorus and calcium in chicken [49]. A recent study showed that *Phaeodactylum tricornutum* (PE) extract encapsulated with alginate-casein (A-C-PE:PE) and chitosan (A-C-PE) showed a controlled release of fucoxanthin and improved adsorption (1.8-fold) using Caco-2/TC7 cells compared to control. *In vivo* experiments further demonstrated the significant bioavailability of fucoxanthin in blood plasma compared to the control PE [174]. Others have recently encapsulated vitamin A in FDA-approved basic methacrylate copolymer to curb the menace of vitamin A deficiency [175]. The results showed that encapsulated vitamin A was thermostable during simulated cooking conditions with concomitant longer shelf life when compared to the free vitamin A. In addition, cooked and light-irradiated encapsulated vitamin A was highly bioaccessible compared to the free-treated vitamin [175]. The above studies demonstrate

that encapsulation does not only protect BASs from environmental factors but also enhances their bioavailability and bioaccessibility consequently maximizing absorption and thus exerting health benefits to human.

## 6. Conclusion

In the context of BASs, encapsulation protects these compounds from degradation and enhances stability, solubility, and bioavailability. It is well documented that many BASs are sensitive to environmental conditions, such as temperature, pH, and light, which can trigger degradation and loss of functional activity. In this article, various methods of BAS encapsulation for food applications were discussed along with their merits and drawbacks. The choice of method depends on the specific application and desired properties of the encapsulated BASs. 3D printing has emerged as a modern trend in BAS encapsulation as it allows for precise and customizable encapsulation of BASs with controlled release properties. Extrusion-based 3D printing is considered cost-effective and scalable method for BAS encapsulation and thus may be used to design personalized functional foods. Encapsulated BASs can be incorporated into inorganic particles and organic-inorganic composites to develop antimicrobial packaging films or nanobiosensors. Inorganic NPs are particularly attractive because of their unique physicochemical properties, including small size and large surface area, which make them ideal candidates for use in antimicrobial films. However, the potential toxicity of some inorganic materials coupled with the lack of transparent and clear nanotechnology regulations limit their application in food encapsulation. Therefore, alternative materials, such as natural and biodegradable polymers, should be explored for safe and effective encapsulation of BASs for food application. Lastly, the various methods of encapsulation enhance bioavailability/bioaccessibility, thus maximizing the absorption potential of encapsulated BASs.

## Conflicts of Interest

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' Contributions

Conceptualization was conducted by D.O.S., A.O.N., N.N.S., P.A., and E.A.N.; D.O.S., A.O.N., N.N.S., P.A., and E.A.N. wrote the original manuscript draft; P.A. and E.A.N. wrote, reviewed, and edited the paper; funding acquisition was conducted by E.A.N. All authors have read and consented to the published version of the manuscript.

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