CHAPTER FOUR

Production of food bioactive-loaded nanoparticles by nano spray drying

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Contents

Nanoencapsulation of Food Ingredients by Specialized Equipment
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1 Introduction

1.1 Bioactive food ingredients market

The global bioactive ingredients market was worth USD 29.8 billion in 2017 according to Research and Markets (2017), and it is projected to grow with about 6.6% to USD 41.1 billion by 2022. The market for encapsulated bioactive and nutraceutical ingredients for functional foods and dietary supplements is largely driven by consumer interest to promote health, well-being, and prevention of disease. People are becoming more aware of the type and source of food and beverages they need for a healthy diet.

After isolation from the original food source, a concentrated extract of the bioactive compound is achieved, and the bioactive ingredients are purified, dried, and then added back into food products to replenish the loss of the component during processing, or they are introduced into foods in which they are typically not present, for example, to create a functional food product or a dietary supplement.

Table 1 lists some major bioactive ingredients of interest to the food and nutraceutical industries including the following (Augustin & Sanguansri, 2017; Garti & McClements, 2012; Gibbs, Kermasha, Alli, & Mulligan, 1999; McClements, 2015):

Table 1 A selection of bioactive food ingredients of interest for the food and nutraceutical industries with potential health effects (Augustin & Sanguansri, 2017; Garti & McClements, 2012; Gibbs et al., 1999; McClements, 2015).

Bioactive food ingredient	Examples	Natural sources	Potential health effects
Omega-3 fatty acids	α-Linolenic acid (ALA)	Flax, perilla, chia	Promoting cardiovascular health
	Eicosapentaenoic acid (EPA) and dodecahexaenoic acid (DHA)	Fish oil, marine algae, krill oil	
Probiotics	Lactobacilli, bifidobacterium	Cultured microorganisms	Improving gut health and immune modulation
Prebiotics	Inulin, oligosaccharides	Chicory root, Jerusalem artichoke, jicama	Promoting gut health and modulation of gut microflora
	β-Glucan	Barley, oats	

Table 1 A selection of bioactive food ingredients of interest for the food and nutraceutical industries with potential health effects (Augustin & Sanguansri, 2017; Garti & McClements, 2012; Gibbs et al., 1999; McClements, 2015).—cont'd

Bioactive food ingredient	Examples	Natural sources	Potential health effects
Carotenoids	β-Carotene	Carrots, sweet potato, palm oil, algae	Reducing risk of diseases and certain cancers
	Lycopene	Tomato, watermelon, red grapefruit	
	Astaxanthin	Green algae	
	Lutein and zeaxanthin	Nastarium (yellow flowers), kale, spinach	
Phenolic compounds	Resveratrol	Japanese knotweed, wine	Reducing risk of cardiovascular disease, cancer, diabetes, and age-related degenerative diseases
	Curcumin	Turmeric	
	Flavonoids (quercetin and rutin)	Onions	
	Flavonoids (hesperidin)	Orange juice	
	Catechins and epicatechins	Cocoa, chocolate, tea	
Essential minerals	Calcium, iron, selenium	Soils, vegetables, water	Maintaining proper human health
Bioactive proteins, peptides, and amino acids	Milk-derived peptides	Milk products	Reducing blood pressure, acting as growth factors, protecting degradation in the gastrointestinal (GI) tracts
Extracts from herbs and spices	Essential oils, various herbal preparations, saffron	Various herbs and spices	A wide range of health benefits

- flavors (e.g., to control taste or aroma of food products)
- antioxidants (e.g., to retard the rate of oxidation in foods)
- antimicrobials (e.g., to inhibit the growth of microorganisms)
- bioactive lipids (e.g., healthy oils, fatty acids, carotenoids, and oil-soluble vitamins)
- bioactive proteins, peptides, and amino acids
- bioactive carbohydrates (e.g., to reduce cholesterol by dietary fibers)
- pre- and probiotics (e.g., to improve gut health)
- essential minerals (e.g., to maintain proper health)
- extracts from herbs and spices

1.2 Colloidal delivery systems for bioactive food ingredients

Due to sensitivity of bioactive ingredients to undesirable environmental influences such as temperature, light, and oxidation, it is important to select an appropriate delivery system and a processing method to maintain their stability and thus their bioactivity. The R&D community is very active in developing new delivery systems for food bioactive ingredients and nutraceuticals in the last couple of years including nanoemulsions, nanostructured lipid carriers, solid lipid nanoparticles, nanosized liposomes, biopolymeric nanoparticles, and micelles made of proteins, polysaccharides, and their complexes or conjugates (Jafari, 2017).

Fig. 1 gives an overview of the variety of colloidal delivery systems available to encapsulate, protect, and control the release of bioactive food ingredients. A challenge is to decide which delivery system to select for a particular food application. In principle, delivery systems for bioactive food ingredients can be formed from different food-grade materials with different processing technologies. The production process has to be economical, reproducible, and robust (Garti & McClements, 2012; McClements, 2015).

The materials used for encapsulated formulations as carrier or matrices typically include a range of proteins (e.g., caseins, whey proteins, soy proteins, wheat proteins), sugars, starches (e.g., maltodextrins), gums (e.g., gum acacia, alginate, pectin, carrageenan), cellulosic materials, chitosan, oils and fats, phospholipids, and food-grade emulsifiers (e.g., Tweens) (Augustin & Sanguansri, 2017).

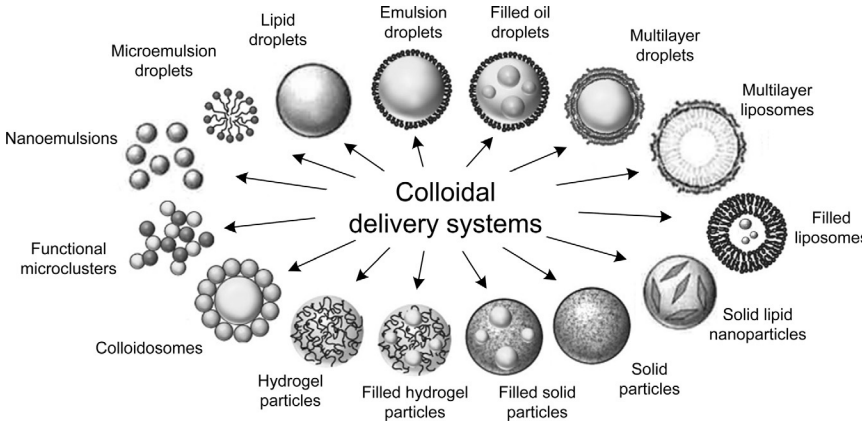

Fig. 1 Examples of different kinds of colloidal delivery systems for encapsulation, protection, and delivery of functional food ingredients.

1.3 Processing technologies, nanotechnology, and encapsulation

Nanotechnology and encapsulation are the two emerging technologies that enable food scientists to realize many innovations in the segment of functional food production. Recent developments in nanoparticle and microparticle delivery systems are revolutionizing colloidal delivery systems in the food industry (Anandharamakrishnan, 2014a; Ezhilarasi, Karthik, Chhanwal, & Anandharamakrishnan, 2013; Garti & McClements, 2012; Jafari, 2017; Jafari, Fathi, & Mandala, 2015; Jafari & McClements, 2017; Livney, 2017; McClements, 2015; Quintanilla-Carvajal et al., 2010).

The nanoencapsulation technologies to fabricate such delivery systems are typically classified into top-down approaches that consist in decreasing the size of macrostructures down to the nanosize scale (e.g., homogenization, dispersions, grinding, injection, and spraying), bottom-up techniques in which arrangements of atoms, molecules, or single particles are induced (e.g., assembly processes) or combined approaches.

The main aims of encapsulating bioactive food ingredients are as follows (Fang & Bhandari, 2012, chap. 12):

- protection from chemical, physical or biological degradation processes
- masking of flavors
- targeted and controlled release of the bioactive food ingredients at a specific location

- extension of shelf life
- improvement of handling and usage
- increase of bioavailability and solubility

The most commonly applied processing technologies for nanoencapsulation and delivery systems of bioactive food ingredients are spray drying, spray cooling/chilling, freeze-drying, fluidized bed coating, extrusion technologies, emulsification, coacervation, liposome encapsulation, and cyclodextrin encapsulation, as outlined in many reviews and books (Anandharamakrishnan, 2014a, 2014b; Anandharamakrishnan & Ishwarya, 2015a; Arpagaus, Collenberg, Rütti, Assadpour, & Jafari, 2018; Arpagaus, John, Collenberg, & Rütti, 2017, chap. 10; Celli, Ghanem, & Brooks, 2015; De Vos, Faas, Spasojevic, & Sikkema, 2010; Ezhilarasi et al., 2013; Fang & Bhandari, 2012, chap. 12, 2017; Garti & McClements, 2012; Grumezescu, 2016; Jafari, 2017; Jafari et al., 2015; Jafari, Paximada, Mandala, Assadpour, & Mehrnia, 2017, chap. 2; Livney, 2017; Ray, Raychaudhuri, & Chakraborty, 2016).

Despite the very active R&D community working on colloidal delivery systems, the list of encapsulation technologies with industrial real usage is surprisingly short, especially when considering natural flavors that are widely used in nutrition. Based on a market analysis by Porzio (2007, 2008) and subjective experiences by Garti and McClements (2012), about 78% of the market of the most commonly employed flavor delivery systems was covered by spray drying, with the remaining portions mostly dominated by melt extrusion, emulsification, fluidized bed coating, plating, coacervation, and others (Fig. 2).

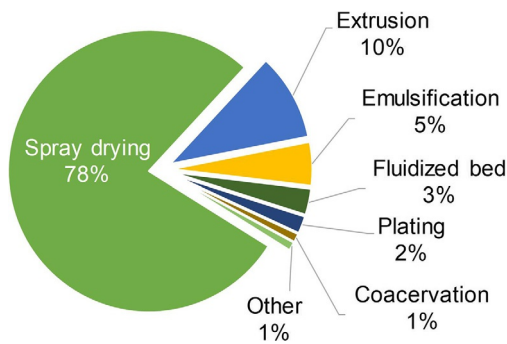

Fig. 2 Estimated worldwide production of flavor delivery systems structured by processing technologies. Spray drying is the most important commercial encapsulation processing technology for flavors. *(Data adapted from Garti, N., McClements, D.J. (2012). Encapsulation technologies food ingredients and nutraceuticals. Cambridge, UK: Woodhead Publishing).*

1.4 Benefits of spray drying for the encapsulation of bioactive food ingredients

Spray drying is a simple, fast, continuous, scalable, and cost-effective drying technology that is very well established in the food industries. Spray drying has been employed for decades to effectively encapsulate a wide range of food bioactive ingredients such as vitamins, minerals, salts, colorants (Akhavan Mahdavi, Jafari, Assadpoor, & Dehnad, 2016; Akhavan Mahdavi, Jafari, Assadpour, & Ghorbani, 2016; Mahdavee Khazaei, Jafari, Ghorbani, & Hemmati Kakhki, 2014), flavors (Esfanjani, Jafari, Assadpoor, & Mohammadi, 2015; Gharsallaoui, Roudaut, Chambin, Voilley, & Saurel, 2007; Rajabi, Ghorbani, Jafari, Mahoonak, & Rajabzadeh, 2015), spices (Jafari, He, & Bhandari, 2007a), fish oils (Mehrad, Shabanpour, Jafari, & Pourashouri, 2015; Pourashouri et al., 2014a, 2014b), lipids, polyphenols, carotenoids (Rostamabadi, Falsafi, & Jafari, 2019), antioxidants (Jafari, Ghalegi Ghalenoei, & Dehnad, 2017; Murugesan & Orsat, 2012), probiotic living cells (Celli et al., 2015; De Vos et al., 2010), proteins, peptides, and enzymes (Abdel-Mageed et al., 2019; Bürki, Jeon, Arpagaus, & Betz, 2011; Dahili & Feczkó, 2015; Sarabandi, Sadeghi Mahoonak, Hamishekar, Ghorbani, & Jafari, 2018). Spray drying technology is still gaining increasing interest due to its wide range of applications. Numerous reviews, research reports, and books have been published on the application of spray drying in the food industries. Table 2 summarizes the main benefits of spray drying technology for encapsulating bioactive food ingredients.

The spray-dried powder form offers high stability; protection of the bioactive food ingredients from oxidation, light, and temperature; easier handling and storage; and redispersibility in aqueous solutions. Spray drying can handle both water- and oil-soluble delivery systems equally well. The produced powders have typically a low moisture content, which increase the food shelf life during storage (Ray et al., 2016). The rapid evaporation of the solvent (e.g., water) during spray drying creates a cooling effect and keeps the droplet temperature relatively low (i.e., below the outlet drying gas temperature); thus, it is possible to produce encapsulated products with heat-sensitive bioactive cores (Murugesan & Orsat, 2012). Spray drying equipment is readily available by many suppliers in the laboratory, pilot, and production scale. Compared with other drying technologies like freeze-drying, the production cost of spray drying is about 30 to 50 times smaller (Arpagaus et al., 2017, chap. 10; Celli et al., 2015; Gharsallaoui et al., 2007).

Table 2 The main benefits of spray drying for the encapsulation of food bioactive ingredients, summarized from various literature (Anandharamakrishnan, 2014b; Anandharamakrishnan & Ishwarya, 2015a, 2015b, chap. 8; Arpagaus, 2007; Arpagaus et al., 2018, 2017, 2013, chap. 18; Arpagaus & Schwartzbach, 2008; Assadpour & Jafari, 2017, 2019; Assadpour, Jafari, & Maghsoudlou, 2017; Augustin & Sanguansri, 2017; Celli et al., 2015; Esfanjani et al., 2015; Fang & Bhandari, 2017; Faridi Esfanjani & Jafari, 2016; Gharsallaoui et al., 2007; Jafari, Assadpoor, Bhandari, & He, 2008, Jafari, Assadpoor, He, & Bhandari, 2008, Jafari et al., 2007a; Li et al., 2015; Mahdavi et al., 2014; Masters, 1991; Murugesan & Orsat, 2012; Nandiyanto & Okuyama, 2011; Porzio, 2007; Rajabi et al., 2015; Sosnik & Seremeta, 2015; Suna et al., 2014; Thybo, Hovgaard, Lindeløv, Brask, & Andersen, 2008; Wong & John, 2015).

Main benefits of spray drying technology for the encapsulation of food bioactive ingredients

- High flexibility to control of particle size, shape, and morphology (e.g., amorphous/crystalline form and porosity)
- One-step process to directly transform various liquid feeds (e.g., solutions, emulsions, suspensions, and slurries) into dry powders
- Process simplicity and ease of operation
- Possible encapsulation of highly sticky feeds with drying aids and surfactants
- Low operating costs, energy-efficient technology, and a fast process
- Scale-up capability (it is one of the oldest processes for the encapsulation of food ingredients, technology is well established, and equipment is readily available)
- Open- or closed-cycle design for aqueous or organic solvents
- Suitable for drying of heat-sensitive bioactives with a low risk of degradation
- Possibility of working with highly viscous feeds through preheating
- Design of particles with controlled release properties
- Applicable to both hydrophilic and hydrophobic food ingredients
- High encapsulation efficiency and extended shelf life for the obtained powders
- Versatile technique with numerous applications and applicability of various design of experiment (DOE) techniques for optimizing the process

Although widely used, spray drying also has some disadvantages. Some authors argue that spray drying is more of an immobilization than a true encapsulation technology, as some of the bioactive agents may be exposed at the surface (Celli et al., 2015). This can be a problem for probiotics, for example, as they can leak from the capsule into the product and affect their viability. Some loss of volatile oils and flavors during spray drying encapsulation seems to be inevitable. Reducing the infeed emulsion size to the nanoscale (about 100 to 300 nm) and thereby increasing the difference between emulsion size and spray-dried powder size are a key in achieving encapsulated spray-dried powders with high retention of volatile oil, low unencapsulated oil at the surface, and maximum encapsulation efficiency

(Jafari et al., 2007a; Jafari, Assadpoor, Bhandari, & He, 2008; Jafari, Assadpoor, He, & Bhandari, 2008; Jafari, He, & Bhandari, 2007b). Another drawback can be too high temperatures used for spray drying. The heat can cause cracks on the surface of the particles, which can adversely affect the stability of the encapsulated bioactive ingredients (Celli et al., 2015). Nevertheless, evaporation of the water from the droplets is very fast, at most in the range of a few seconds, and the particle surface exposed to the heat remains below the outlet drying gas temperature.

1.5 Wall materials, particle morphology and particle size range

The selection of a suitable wall material for nanoencapsulation is based on similar factors as for microencapsulation (Gharsallaoui et al., 2007). Relevant criteria include compatibility with the encapsulated bioactive component, suitable release properties, high encapsulation efficiency, mechanical strength, storage stability, easy emulsifiability, water solubility, and edibility. The ideal wall material should have (Jafari, Assadpoor, He, & Bhandari, 2008)

- emulsifying properties,
- be a good film former and oxygen barrier,
- low viscosity a high solid levels,
- exhibit low hygroscopicity,
- controllable release properties,
- be low in cost,
- bland in taste.

Different types of food-grade carriers and encapsulating wall materials are used for spray drying of bioactive food ingredients. Table 3 presents a brief summary of wall materials along with their encapsulation-related properties. The major wall materials used are carbohydrates (e.g., starches, maltodextrins, gum arabic, and cyclodextrins), proteins (e.g., whey proteins, caseinates, and gelatin), and other biopolymers (Fang & Bhandari, 2012, chap. 12, 2017). Maltodextrin and gum arabic are the classical wall materials used for the encapsulation of essential oils by spray drying. A typically adopted core to wall material ratio is 1:4 (20% core material) (Arpagaus, 2007; Büchi Labortechnik AG, 2002; Jafari, Assadpoor, He, & Bhandari, 2008; Jafari et al., 2007a; Ray et al., 2016).

As shown in Fig. 3, various morphologies of encapsulated powders can be obtained by spray drying such as single-core, irregular, multiwall, multicore, composites, and pure bioactives. The particle surface can be either smooth and spherical, collapsed, dimpled, wrinkled, raisin-like, highly

Table 3 Commonly used wall materials and their properties for spray drying encapsulation.

Wall material	Example	Encapsulation-related properties
Carbohydrates	Hydrolyzed starches (corn syrup solids, maltodextrins, etc.)	• Very good oxygen barrier • Low viscosity at high solids • No/limited emulsion stabilization • Low cost
	Modified starches (acetylated starch, monostarch phosphate, etc.)	• Sometimes varying quality • Constricted usage due to regulatory situation • Low cost
	Gums: agar, gum arabic, sodium alginate, etc.	• Good emulsion stabilization • Good retention of volatiles • Varying quality • Constricted usage due to regulatory situation • Sometimes impurities • Low cost (price depends on availability)
	Cyclodextrins: α-, β-, γ-cyclodextrins	• Good inclusion of volatiles • Excellent oxygen barrier • Relatively expensive
Proteins	Milk proteins: whey proteins, caseinates, skim milk powders Other proteins: soy protein, egg protein, gelatin	• Good emulsions • Properties depend on other factors such as pH and ionic strength • Allergenic potential • Relatively expensive
Other biopolymers	Soluble soy polysaccharides, chitosan, Maillard reaction products, modified celluloses	• Varied properties • May provide additional benefit to the stability of bioactives

From Fang, Z., Bhandari, B. (2017). Spray drying of bioactives. In Y. H. Roos & Y. D. Livney (Eds.), *Engineering foods for bioactives stability and delivery, Food engineering series* (pp. 261–284). New York, NY: Springer New York; Fang, Z., Bhandari, B. (2012). Encapsulation techniques for food ingredient systems. In B. Bhandari & Y. H. Roos (Ed.), *Food materials science and engineering* (pp. 320–348). Blackwell Publishing Ltd. with permission.

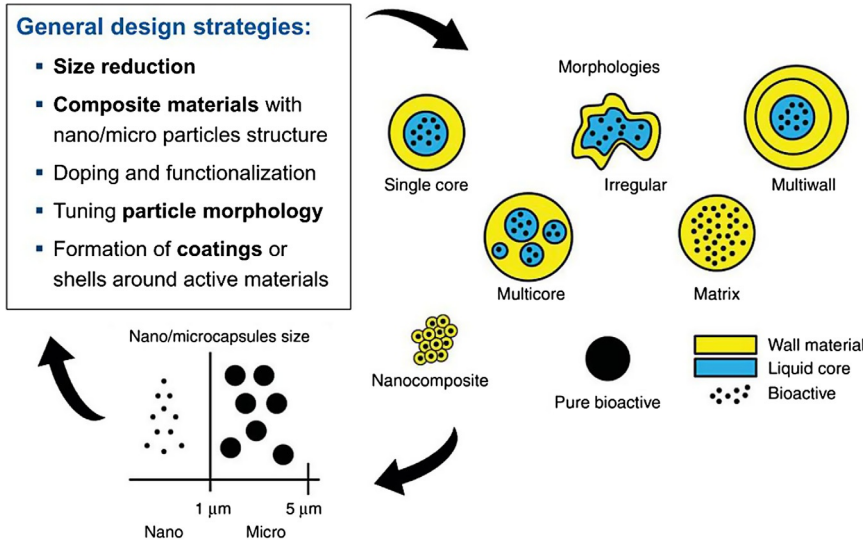

Fig. 3 Different particle morphologies and size ranges (Arpagaus, 2018a; Arpagaus et al., 2017).

crumpled, or folded (Arpagaus, 2018a; Arpagaus et al., 2017; Esfanjani et al., 2015; Mahdavi, Jafari, Ghorbani, & Assadpoor, 2014; Nandiyanto & Okuyama, 2011).

The sizes of the particles formed through encapsulation can be classified into macro (>5 mm), micro (1 µm to 5 mm), and nano (<1 µm) (Fang & Bhandari, 2012). Nanoparticles are commonly defined as solid colloidal particles with sizes below 1 µm (Kaialy & Al Shafiee, 2016; Lee, Heng, Ng, Chan, & Tan, 2011; Li, Anton, Arpagaus, Belleteix, & Vandamme, 2010; Wong, 2015; Wong & John, 2015). Capsules smaller than 1 µm in diameter are known as nanocapsules (Arpagaus et al., 2017; Couvreur, Dubernet, & Puisieux, 1995; Jafari, Assadpoor, Bhandari, & He, 2008; Jafari, Assadpoor, He, & Bhandari, 2008; Jafari et al., 2007a). Nanocapsules, due to their smaller size and larger specific surface, offer higher absorption rates and bioavailability of the encapsulated bioactive food ingredient compared with microcapsules (Lee et al., 2011).

According to the studies of Friends of the Earth (2008, 2014), the number of nanofood products has increased more than 10-fold in the last 6 years. A list of some 200 foods and beverages known to contain nanomaterials could be compiled. Besides the many benefits of nanomaterials, the formulation of nanoparticles involves certain risks, such as potential toxicological hazards. Therefore, it is crucial to be sure about product safety before

releasing a new nanofood ingredient onto the market (Arpagaus, 2009). Nanomaterials must be tested as if they were completely new substances, and it is necessary to look at each individual case in detail. For spray-dried nanoproducts, it is recommended to conduct feasibility studies in laboratory-scale first with small powder amounts, and if an ingredient receives the green light for launch to consumers, the spray drying technology can then be scaled-up on an industrial basis.

1.6 Nano spray drying

The recent rise in nanotechnological applications in foods particularly in the area of food functionality like enriched and fortified food products in particulate dosage form (Grumezescu, 2016; Oprea & Grumezescu, 2017) has increased the pressure on existing spray drying systems to produce nanoparticles with a high yield and a narrow size distribution.

A remarkable growth of the research activity in the field of nano spray drying can be recognized in the past 20 years. A literature search in the online databases of Web of Science and SCOPUS with the topic "nano spray drying" resulted 658 and 720 hits, respectively, from the years 1997 to 2017 (Fig. 4). For instance, the number of publications increased to approximately 100 in 2017. Considerable research activities on nano spray drying are taking place worldwide, particularly in the fields of pharmaceuticals, materials technology, and bioactive food ingredients. Obviously the potential of nano spray drying has not yet been fully exploited. Compared with traditional spray drying in the micrometer scale, the current level of nano spray drying is still in its infancy (Assadpour & Jafari, 2019), but it is generally expected that more and more products will be developed in the coming years.

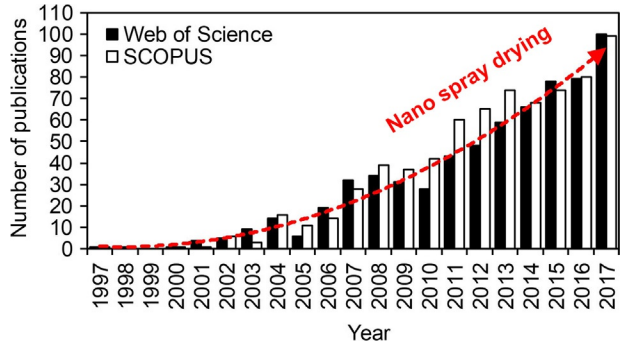

Fig. 4 Number of papers published in the online databases of Web of Science (http://www.webofscience.com) and SCOPUS (http://www.scopus.com) with the topic "nano spray drying" since 1997 (accessed on December 31, 2018).

Nanoscale powders by spray drying represent a new platform for many applications in food technology (Arpagaus, 2009).

Several excellent reviews on spray drying technology for nanoparticle formation have already been published (Nandiyanto & Okuyama, 2011; Okuyama, Abdullah, Lenggoro, & Iskandar, 2006; Okuyama & Lenggoro, 2003; Sosnik & Seremeta, 2015; Wang, Zhang, Zhang, Mujumdar, & Huang, 2005) and in particular on nano spray drying technology (Arpagaus, 2012, 2018a, 2018b, 2018c; Arpagaus et al., 2018, 2017, chap. 10; Assadpour & Jafari, 2019; Heng, Lee, Ng, & Tan, 2011; Lee et al., 2011; Suna, Sinir, & Çopur, 2014).

1.7 Objectives of this chapter

This chapter explains the specialized technology of nano spray drying for stabilizing bioactive food ingredients. First, the laboratory product Nano Spray Dryer B-90 developed by the Swiss company Büchi Labortechnik AG is presented with focus on explaining the essential technological and practical aspects of the nano spray drying process.

The second section discusses the influence of process parameters on the respective powder properties for successfully nano spray drying of bioactive food ingredients. In particular, the chapter highlights the way of reducing the size of spray-dried particles by an order of magnitude to reach submicron sizes.

The final part gives an overview of recent food and nutraceutical applications performed on a laboratory scale. The encapsulation of bioactive food ingredients in several polymeric wall materials with a high encapsulation efficiency is presented. In particular, the potential of nanoemulsions and solid lipid nanoparticles as colloidal delivery systems for nano spray-dried formulations is demonstrated.

Overall, this chapter attempts to summarize the most important findings of the last 15 years on nano spray drying of bioactive food ingredients.

2 Nano spray drying technology

2.1 Process steps

The process steps of a nano spray dryer are essentially the same as in a traditional spray dryer, which includes

(1) heating of the drying gas,

(2) droplet formation by atomization of the fluid supply,

(3) drying of the droplets in the drying gas and formation of dry particles,

(4) particle separation and collection of the dry particles from the drying gas.

However, compared with a traditional spray dryer, some technological modifications on the experimental setup are necessary to produce and collect nanoscale particles, that is,

(1) the nozzle system should be able to produce smaller droplets;
(2) the drying gas flow needs to be gentle, laminar, and cocurrent with the sprayed droplets; and
(3) the particle collector must be highly efficient in separating submicron particles.

In 2009, the Swiss company Büchi Labortechnik AG launched the laboratory product Nano Spray Dryer B-90 for producing small quantities of submicron powders in the gram scale with very narrow distributions and high yields (Arpagaus, 2009; Arpagaus, Friess, & Schmid, 2009). Fig. 5 shows the setup and explains the implemented technologies for spray generation, heating of the drying gas, and particle collection.

2.2 Droplet generation by vibrating mesh technology

The droplet generation is based on vibration mesh technology, which has been adapted from nebulizers for inhalation therapy to the nano spray dryer application (Dhand, 2002; Knoch & Keller, 2005; Lass, Sant, & Knoch, 2006; Smart et al., 2002; Vecellio, 2006). Fig. 6A shows an exemplary picture of the generated spray of droplets and (B) to (E) some microscopic images of the holes in a spray mesh. The spray head is connected by plastic tubes to the feed reservoir, and a peristaltic pump with variable speed circulates the fluid uniformly through the spray head into the spray mesh and back to the reservoir (see Fig. 5). This circulation mode enables efficient and continuous atomization.

An electronically driven piezoelectric actuator vibrates the thin spray mesh that contains an array of laser drilled micron-sized holes in the center (approximately 1500 holes in a 5.5-μm spray mesh). The holes have a conical shape with about 50-μm diameter toward the fluid supply side and a narrow diameter (i.e., 5.5 μm) facing the front of the droplet release. Spray meshes are available with 4.0-, 5.5-, and 7.0-μm holes (first-generation spray head). The second generation of vibrating mesh technology in the Nano Spray Dryer B-90 HP launched in 2017 offers optimized productivity and better handling during installation and replacement. These nebulizers are available in small, medium, and large size.

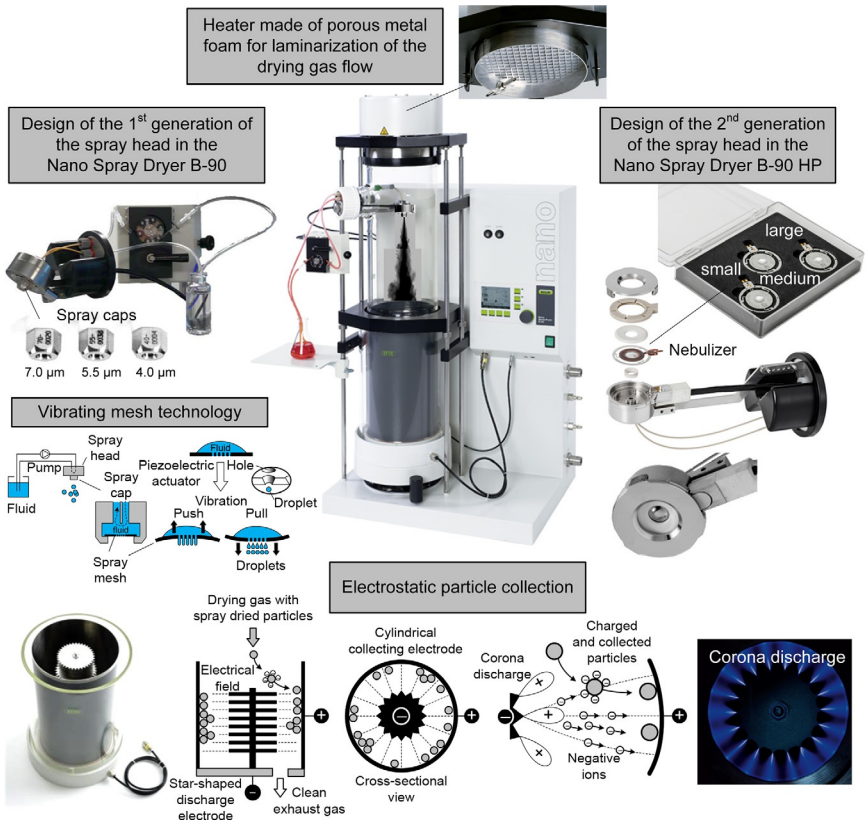

Fig. 5 Nano Spray Dryer B-90 (short setup) with the first and second generation of vibrating mesh technology for spray generation, the electrostatic particle collector, and the heater made of porous metal foam for gas laminarization. *(Pictures courtesy of Büchi Labortechnik AG).*

The vibration at ultrasonic frequency, which is adjustable from 80 to 140 kHz, deforms the mesh into the fluid side, loads the holes with fluid, and pushes the fluid through the mesh into the drying chamber. The output is fine low-velocity droplets with very narrow size distribution optimized for nano spray drying. At a vibration frequency of 100 kHz and 1000 active holes in the spray mesh, approximately 100 million precisely dimensioned droplets are produced per second. The uniformity of the droplet size is mainly defined by the uniformity of the holes. The droplet size depends on the mesh size and the physicochemical properties of the fluid, such as viscosity and surface tension. The mean droplet size of water is approximately 4.8, 6.2, and 7.2 µm (SPAN $(d_{90} - d_{10})/d_{50}$ from 1.1 to 1.3, reproducibility

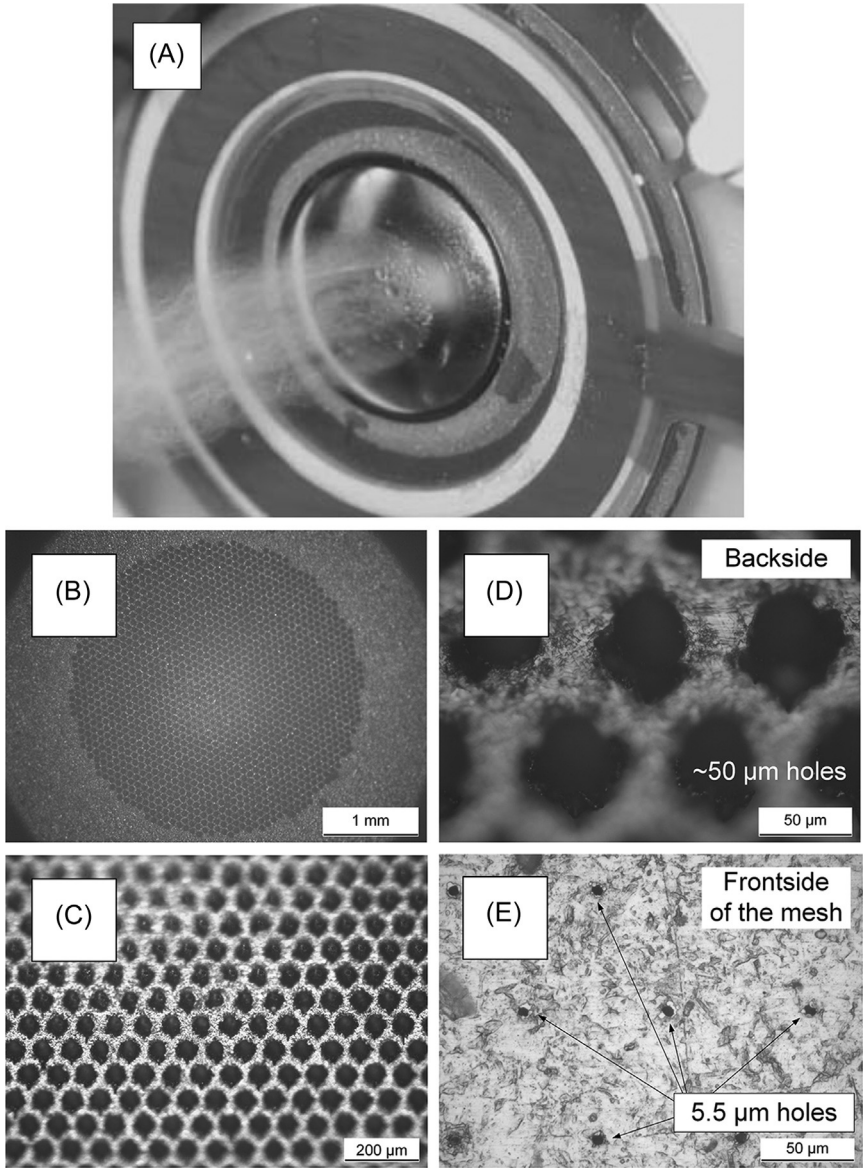

Fig. 6 Vibrating mesh atomizer with perforated metallic membrane. (A) Picture from TouchSpray (eFlow) illustrating the generated spray of droplets (Geller, 2008). A low-velocity mist is generated through the holes. (B) Microscopic backside view of a 5.5-µm spray mesh (in contact with the liquid feed reservoir) with approximately 1500 precise tapered laser drilled holes (Nano Spray Dryer B-90). (C) and (D) Higher resolutions of the backside of the spray mesh. (E) Frontside view of the spray mesh (toward the drying chamber) with 5.5-µm holes.

Table 4 Droplet size of water sprayed with spray meshes of 4.0, 5.5, and 7.0 μm hole size (determined by laser diffraction).

Spray mesh (μm)	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)	SPAN $(d_{90} - d_{10})/d_{50}$
4.0	3.3	4.8	8.5	1.11
5.5	4.4	6.2	11.5	1.15
7.0	5.2	7.2	14.7	1.32

Data from Arpagaus, C., John, P., Collenberg, A., Rütti, D. (2017). Nanocapsules formation by nano spray drying. In S. M. Jafari (Ed.), *Nanoencapsulation technologies for the food and nutraceutical industries* (pp. 346–401). Elsevier Inc.; Schmid, K., 2011. *Spray drying of protein precipitates and evaluation of the nano spray dryer B-90* (Ph.D. thesis). Munich: Ludwig-Maximilians-University; Schmid, K., Arpagaus, C., Friess, W. (2011). Evaluation of the nano spray dryer B-90 for pharmaceutical applications. *Pharmaceutical Development and Technology 16*, 287–294.

±0.5 μm) using spray mesh 4.0, 5.5, and 7.0 μm (see Table 4) (Arpagaus et al., 2017, chap. 10; Schmid, 2011; Schmid, Arpagaus, & Friess, 2011).

A limitation of the vibrating mesh technology is the risk to clog some of the tiny holes in the spray mesh if the product is too concentrated or if the primary particle sizes in the fluid are bigger than about 1/10 of the nebulizer hole diameter (i.e., particles > about 0.4 to 0.7 μm). Some solutions may be too viscous to pass through the mesh, for example, sodium carboxymethyl cellulose, which is a strong viscosifier (Oliveira, Guimarães, Cerize, Tunussi, & Poço, 2013). This may result in intermittent droplet generation or even cessation of droplet generation. The maximum liquid viscosity is about 5 to 10 mPa s (Arpagaus, Schafroth, & Meuri, 2010a). Obviously, regular cleaning of the spray mesh and nebulizer is necessary to maintain the efficient function of the mesh. It is recommended to clean the spray mesh and nebulizer in an ultrasonic bath for 1 to 2 min. Moreover, it is considerable using a lower sample concentration, filtering of the feed solution, or changing to a larger nebulizer. As stated by Schmid (2011), virtually any substance can be nano spray-dried successfully as long as the correct test arrangement is used (i.e., solvent, solid concentration, feed composition, and drying conditions).

2.3 Laminar drying conditions

The drying gas is heated up to the set inlet temperature (T_{in}) in a compact heater at the top of the nano spray dryer. The heating unit consists of a porous metal foam with an embedded electrical heating coil (Fig. 7). This coil ensures efficient heat transfer to the metal foam and uniform heat distribution in the entire heating volume. The porous metal surface generates a laminarization of the gas flow for gentle drying of the sprayed droplets. This

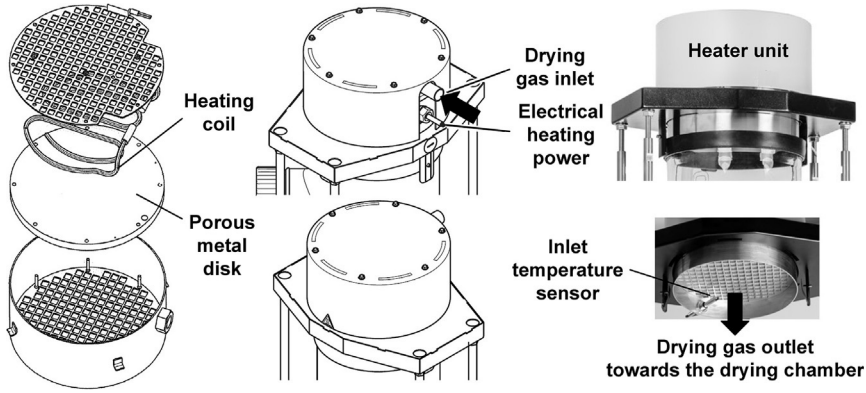

Fig. 7 Compact heater unit at the top of the Nano Spray Dryer B-90 consisting of an electrical heating coil pressed into a porous metal foam for laminarization of the drying gas. *(Pictures courtesy of Büchi Labortechnik AG, Patent EP 2056037 A1, Schön, M., & Baumgartner, R. (2009).* Apparatus with spray drier and electrostatic separator as well as method for separating particles. *Patent EP 2056037 (A1), priority date: 2007-10-30).*

is crucial because turbulence would lead to uncontrolled spray formation and particle depositions on the sidewalls of the drying chamber. Thus, nano spray drying is a very gentle drying technology suitable for heat-sensitive products with a low risk of degradation or loss of activity.

The modular glass assembly of the drying cylinders allows simple modification of the length of the drying chamber, it is easy to clean, and considerable process time can be saved in daily lab work. The Nano Spray Dryer B-90 can be operated with a short or long version of the drying chamber, which corresponds to approx. 0.32-m and 0.77-m drying length from the spray nebulizer to the particle collector. The drying gas flow rate can be adjusted within a range of 80 to 160 L/min, which is equivalent to gas velocities of 0.05 to 0.1 m/s in the drying chamber (tube inner diameter = 0.18 m). The Reynolds number is between 330 and 660 at 120°C inlet temperature and 40% humid air. The average gas residence time in the drying chamber is about 3–6 s in the short setup and 7 to 15 s in the tall setup, respectively.

2.4 Electrostatic particle collection

A highly efficient electrostatic particle collector separates the dried particles from the gas stream. The electrostatic particle collector consists of a stainless steel cylinder (anode = particle collection electrode) and a star-shaped

counter electrode (cathode) inside the cylinder (see Fig. 5). During the nano spray drying process, a high voltage of approx. 15 kV is applied between the electrodes, and the dried particles are electrically charged deflected to the inner wall of the cylinder electrode. The electrostatic particle collector is able to capture submicron particles (<1 μm) at a separation efficiency >99% for small batches of 10 mg to 2.7 g powder (Arpagaus & Meuri, 2010; Arpagaus, Schafroth, & Meuri, 2010b; Bürki et al., 2011; Lee et al., 2011; Li et al., 2010; Schmid, 2011; Schmid, Arpagaus, & Friess, 2009; Schmid et al., 2011). It can even collect thin-walled particles without breaking (Feng et al., 2011; Sun, Song, Wang, & Yu, 2011).

A special feature of the electrostatic particle collector is a segregation effect over the cylinder length. Larger particles are captured earlier than smaller ones because bigger particles have a larger surface charge and a larger electrostatic force acting on the particles. As a result, the particles collected on the lower part of the collecting electrode are slightly smaller than those collected on the upper part (Brinkmann-Trettenes, Barnert, & Bauer-Brandl, 2014; Li et al., 2010; Suryaprakash, Lohmann, Wagner, Abel, & Varga, 2014). Moreover, the particle deposition is axially symmetrical in the collection cylinder (Brinkmann-Trettenes et al., 2014).

After completion of the nano spray drying process, the fine dried powder particles are gently collected from the inner surface of the collection electrode cylinder using the particle scraper and the particle collection paper included in the scope of delivery of the laboratory instrument (Fig. 8). Finally, the particles are filled into airtight glass vials and stored in a controlled and dry atmosphere (e.g., in a desiccator over silica gel at room temperature) until further usage and examination to prevent crystallization and moisture absorption (Schmid, Arpagaus, & Friess, 2011). Yield fluctuations and minimal losses can occur when collecting powder manually with a scraper.

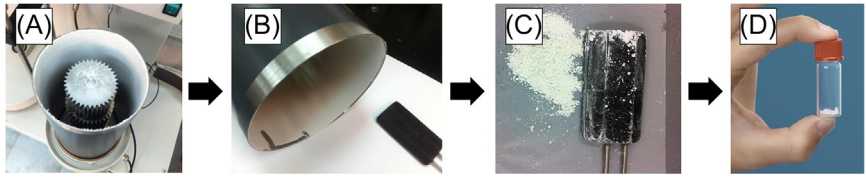

Fig. 8 Particle collection process in the laboratory-scale Nano Spray Dryer B-90. (A) Dried particles deposited on the collection cylinder (minor losses on the star electrode in the center), (B) collection cylinder with particle scraper, (C) manually recovered powder on collecting paper, (D) powder filled in air-tight glass vial.

2.5 Influence of process parameters and formulation variables on powder properties

For nano spray drying of bioactive food ingredients, there are several process parameters that can be varied to optimize the yield, bioactive loading, encapsulation efficiency, particle size, release profile, stability, and morphology (Arpagaus, 2018a, 2018b, 2018c; Arpagaus et al., 2018, 2017; Arpagaus, Rütti, & Meuri, 2013). Fig. 9 illustrates the adjustable process parameters and formulation variables for a nano spray dryer. Table 5 provides an overview of the main process parameters and their influence on the final product properties. The thickness of each arrow illustrates the strength of the relationship.

Depending on the application, an optimized set of process parameters can be found. Design of experiment (DOE) studies are suitable to optimize the nano spray drying conditions, as shown by many researchers (Abdel-Mageed et al., 2019; Arpagaus et al., 2017, chap. 10; Bürki et al., 2011; Draheim, de Crécy, Hansen, Collnot, & Lehr, 2015; Durli et al., 2014; Gu, Linehan, & Tseng, 2015; Harsha et al., 2017; Lee et al., 2011;

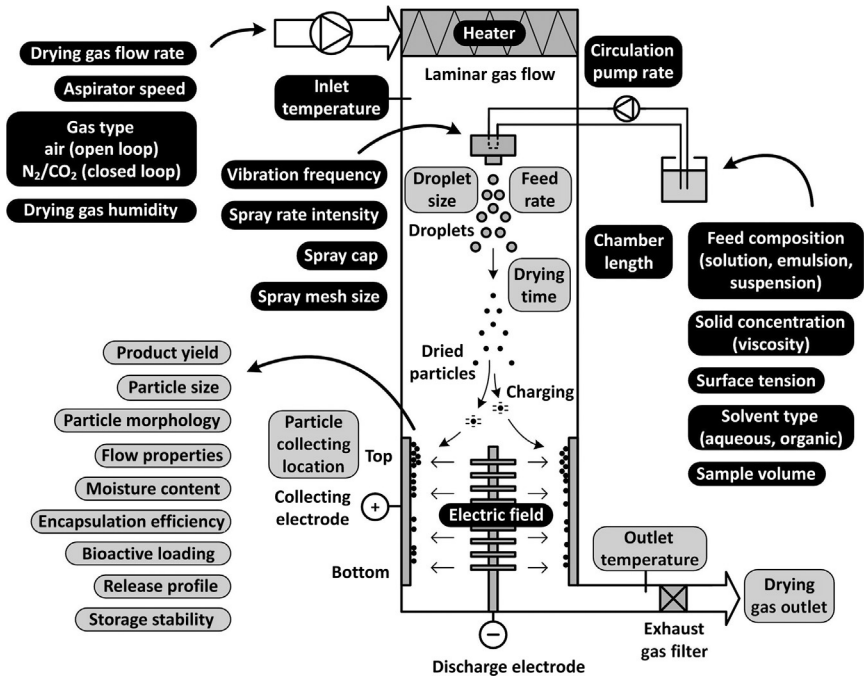

Fig. 9 Process parameters and formulation variables for the production of bioactive food-loaded nanoparticles by nano spray drying (Arpagaus et al., 2018, 2017).

Table 5 Influence of the main process parameters in nano spray drying (⬆/⬇ strong increasing/decreasing influence, ↑/↓ weak increasing/decreasing influence, – minimal or no influence).

Process parameter	Outlet temperature	Droplet size	Particle size	Feed rate	Moisture content	Yield	Stability
Drying gas flow rate ↑	⬆	–	–	–	⬇	–	–
Drying gas humidity ↑	↑	–	–	–	⬆	↓	–
Inlet temperature ↑	⬆	–	↑	–	↓	↑	⬇
Spray mesh size ↑	↓	⬆	⬆	⬆	–	–	↑
Spray frequency ↑	⬇	↑	↑	⬆	↑	–	⬇
Circulation pump rate ↑	–	↑	↑	↑	–	–	↑
Solid concentration (viscosity) ↑	↑	–	⬆	⬇	↓	↑	–
Surfactant/ stabilizer in feed ↑	–	↓	↓	↑	–	↑	⬆
Organic solvent instead of water	⬆	↓	↓	↑	⬇	↑	–

Based on Arpagaus, C., John, P., Collenberg, A., Rütti, D., 2017. Nanocapsules formation by nano spray drying. In S. M. Jafari (Ed.), *Nanoencapsulation technologies for the food and nutraceutical industries* (pp. 346–401). Elsevier Inc.

Li et al., 2010; Littringer et al., 2013; Schafroth, Arpagaus, Jadhav, Makne, & Douroumis, 2012; Schoubben, Giovagnoli, Tiralti, Blasi, & Ricci, 2014).

Assuming a one-to-one transformation of droplets to dried particles, the final particle size (d_P) is directly related to the solid concentration in the feed solution (C_S) and the droplet size (d_D) (Maa, Nguyen, Sit, & Hsu, 1998). The relationship can be approximated by Eq. (1):

$$d_P = d_D \cdot \left(\frac{C_S}{\rho}\right)^{\frac{1}{3}} \tag{1}$$

where ρ is the particle density. The formula assumes spherical droplets and solid nonporous particles, negligible volatile content in the particles, and that all droplets contain the same concentration of solids. C_S is typically in the order of 0.1 to 0.01 g/mL, and ρ is mainly around 0.9 to 1.5 g/cm^3, respectively. Obviously, a smaller spray mesh leads to smaller droplets and consequently to smaller dried particles. The submicron particle size is typically reached when using a 4.0-μm spray cap and diluted solutions of about

0.1% to 1% (w/v), as demonstrated in many studies (Baba & Nishida, 2013; Beck-Broichsitter, Paulus, Greiner, Kissel, 2015; Beck-Broichsitter et al., 2012; Bürki et al., 2011; De Cicco, Porta, Sansone, Aquino, & Del Gaudio, 2014; Lee et al., 2011; Li et al., 2010; Littringer et al., 2013; Nandiyanto & Okuyama, 2011; Ngan et al., 2014; Pérez-Masiá et al., 2015; Schmid, 2011; Schmid et al., 2009, 2011). Table 6 presents some particle size data of food-grade materials, which have been nano spray-dried with different spray mesh sizes and solid concentrations. The SEM images in Fig. 10 show the effect of varying spray mesh size on nano spray-dried particle size and morphology.

Table 6 Influence of spray mesh size and solid concentration on nano spray-dried particle size (– = data not available).

Substance	Solvent	Solid concentration (%, w/v)	Particle size (in nm) obtained with spray mesh			Reference
			4.0 µm	5.5 µm	7.0 µm	
Chitosan (low-density)	0.5% acetic acid	0.025	95	215	265	Ngan et al. (2014)
		0.05	180	–	–	
		0.075	236	–	–	
		0.1	358	–	–	
Ethambutol (bacteriostatic and antituberculosis agent)	Water	1	222	–	–	Ahmad, Ungphaiboon, and Srichana (2014)
Gum arabic	Water	0.1	355	–	–	Li et al. (2010)
		1	580	–	–	
Whey protein	Water	0.1	420	–	–	Li et al. (2010)
		1	595	–	–	
Sodium chloride	Water	0.1	515	–	–	Li et al. (2010)
		1	995	–	–	
Disodium phosphate	Water	0.1	500	–	–	Schmid et al. (2011) and Schmid (2011)
Trehalose	Water	0.1	800	–	–	Schmid et al. (2011) and Schmid (2011)
Bovine serum albumin (with surfactant)	Water	0.1	460	–	–	Lee et al. (2011)
		1	700	1700	2600	
Sodium alginate	Water	0.13	760	–	–	Blasi, Schoubben, Giovagnoli, Rossi, and Ricci (2010)
Curcumin in albumin	Water	0.5	715	–	–	Jain (2014)

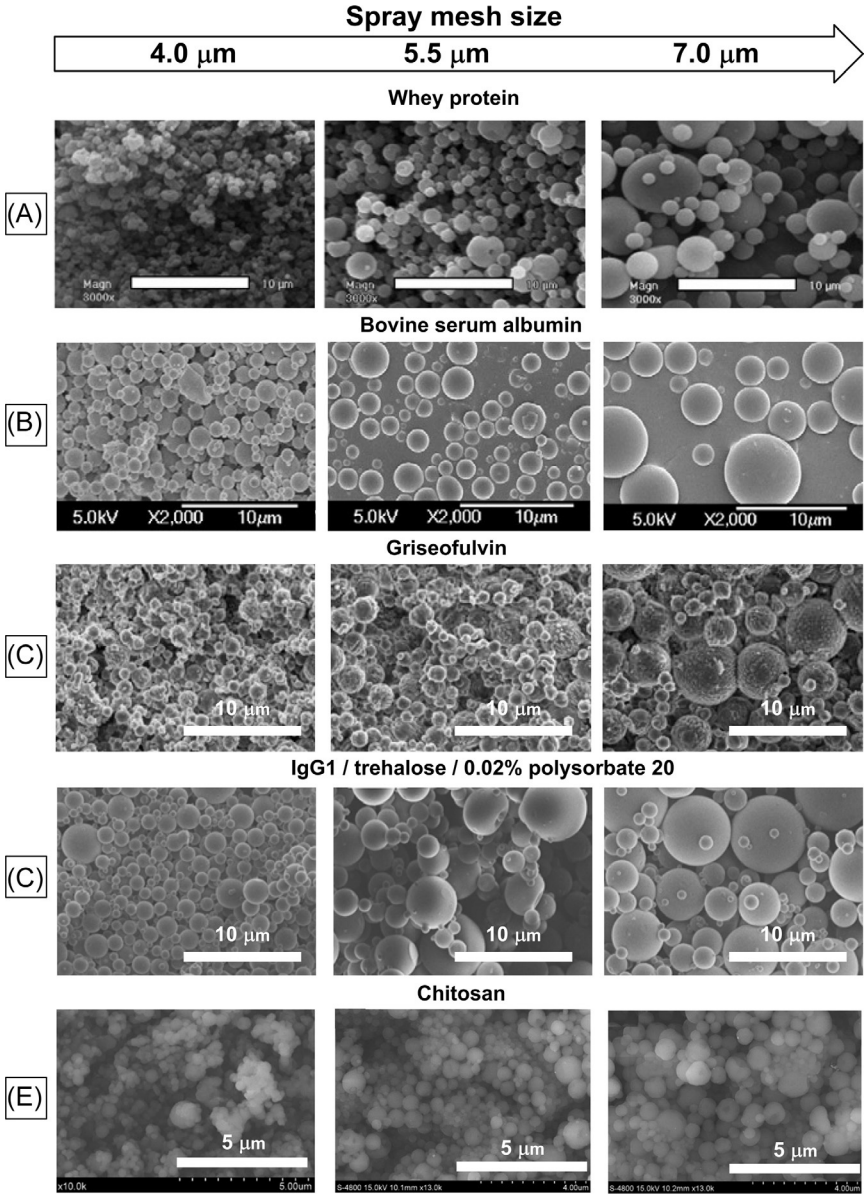

Fig. 10 Effect of the spray mesh size 4.0, 5.5, and 7.0 μm on the dried particle size. (A) Whey protein at 0.1%, 1%, and 10% (w/v) solid concentration (Li et al., 2010), (B) bovine serum albumin at 1%, particle size: 0.7, 1.7, and 2.6 μm (Lee et al., 2011), (C) griseofulvin at 0.5% in methanol/acetone, particle size: 3.4, 4.9, and 6.5 μm (Schmid, 2011), (D) monoclonal IgG_1 antibody in trehalose (2.5%, ratio 70:30) with 0.02% polysorbate 20 (Schmid, 2011), (E) chitosan (276 cP) at 0.025%, particle size: 95, 215, and 265 nm (Ngan et al., 2014).

Other parameters to consider when nano spray drying are the inlet and outlet temperatures of the drying gas, the spray rate of the vibrating mesh atomizer, the drying gas type, the drying gas flow rate, and its humidity. The feed-related parameters, such as the feed composition (e.g., core-to-wall materials ratio, bioactive content, surfactants, emulsifiers, stabilizers, and polymer glass transition temperature), the viscosity, the solid concentration, and the solvent type (e.g., boiling point, aqueous, organic, or mixture), will mainly affect the final powder properties.

As shown schematically in Fig. 11 (left), the droplet temperature in a nano spray dryer rises initially to the saturated wet-bulb surface temperature, remains constant during evaporation (constant-rate drying phase), and approaches the temperature of the surrounding gas at dryer outlet (falling-rate drying phase). The solvent evaporation cools the surrounding drying gas, and the droplet temperature remains constant. As more and more of the solvent evaporates from the droplet, the solid content of the outer layer of the droplet increases to the point where it forms a shell. At this point, a particle with a solid shell but wet core is formed, and the drying phase switches to the falling-rate phase. During this phase, heat is transferred to the particle from the drying gas as sensible heat. The temperature of the particle is raised to fully evaporate the remaining solvent from the core of the particle.

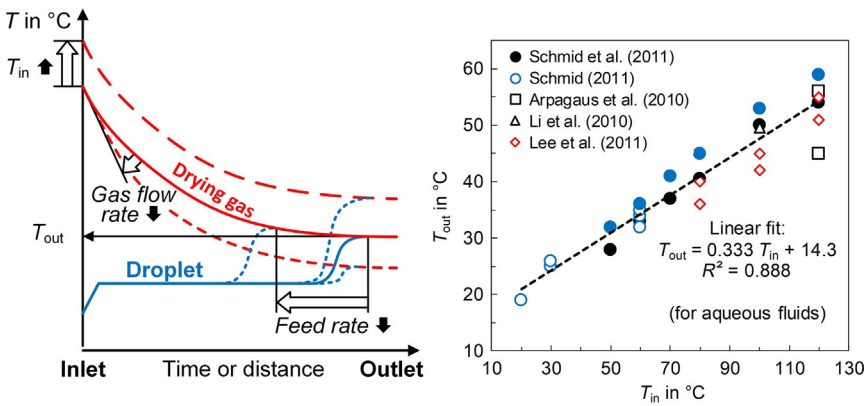

Fig. 11 Typical temperature curve of the drying gas and the droplets during nano spray drying. Left: influence of drying gas temperature, gas flow rate, and feed rate on the droplet temperature. Right: linear fit between the inlet (T_{in}) and outlet (T_{out}) temperature in the Nano Spray Dryer B-90 for aqueous fluids, that is, $T_{out} = 0.333 \cdot T_{in} + 14.3°C$ (Arpagaus, 2018a; Arpagaus et al., 2017).

The outlet temperature of the drying gas is directly related to the set inlet temperature, the flow rate, the sample concentration, and the drying gas flow rate. Changes in any of these parameters will either increase or decrease the outlet temperature. A lower drying gas flow rate leads to a lower outlet temperature; a smaller feed rate increases the outlet temperature. A higher inlet temperature reduces the relative humidity of the drying gas, resulting in a drier and less sticky powder. Residual moisture contents of lower than 0.5% in mannitol, 2% to 5% in trehalose, and 7% for β-cyclodextrin and hydroxytyrosol powders have been observed (Malapert et al., 2019; Schmid, 2011). For aqueous applications, the outlet temperatures are between 28°C and 59°C and follow a linear relationship of $T_{out} = 0.333 \cdot T_{in} + 14.3°C$ as a first approximation (Fig. 11, right) (Arpagaus, 2018a; Arpagaus et al., 2017), which makes nano spray drying a suitable process for heat-sensitive substances (Amsalem et al., 2017; Aquino et al., 2014; Heng et al., 2011).

The estimated drying time of water droplets in a Nano Spray Dryer B-90 is in the order of 10 ms, assuming droplets of 7-μm diameter, 75°C drying temperature, and 100 L/min drying air flow rate (Feng et al., 2011). Because the total residence time of the particles in the nano spray dryer is much longer than the required drying time, the particles are dry when arriving at the electrostatic particle collector.

A compromise needs to be found between feed rate (productivity in mL/min), solid concentration, and particle size. The feed rate increases primarily with the spray mesh size and the setting of the relative spray frequency, and it depends on the feed formulation (i.e., solid concentration, solvent type, and the addition of surfactant) (see experimental data in Table 7).

For pure water, the specified feed rates are in the ranges of 10–20, 25–50, and 80–150 mL/h for a 4.0-, 5.5-, and 7.0-μm spray mesh, respectively (Büchi Labortechnik AG, 2010). A higher solid concentration results in a lower feed rate. The addition of organic solvents or a small amount of surfactant into the feed tends to increase the feed rates, which can be attributed to the lower surface tension.

The yield of nano spray-dried particles can be calculated from the total weight of the recovered particles and the original weight of the bioactive and polymer. Table 8 shows some examples of optimized product yields that typically range from about 43% to 95% for small sample quantities of less than 1 g. Particle losses can be attributed to deposits on the walls of the drying chamber and losses during manual removal of particles from the surface of the electrostatic particle collector.

Table 7 Influence of spray mesh size and solid concentration on the feed rate for aqueous substances at 100% spray rate in the Nano Spray Dryer B-90.

Substance	Solid concentration (%, w/v)	Solvent	Spray mesh size (µm)	Feed rate (mL/h)	Reference
Water	–	Water	4.0	10–20	Büchi
			5.5	25–50	Labortechnik
			7.0	80–150	AG (2010)
Gum arabic, maltodextrin, polyvinyl alcohol, modified starch	1	Water	4.0	3–25	Li et al. (2010)
Trehalose	0.1	Water	4.0	11	Schmid (2011)
	1			8	
	10			5	

Table 8 Examples of optimized yields achieved by nano spray drying for small sample amounts (– = not available).

Product yield (%)	Solid sample amount (mg)	Substance	Reference
43–95	30–300	Gum arabic, maltodextrin, polyvinyl alcohol, modified starch, and whey protein	Li et al. (2010)
75–94	500	α-Amylase enzyme in sucrose and Tween 80	Abdel-Mageed et al. (2019)
60–94	500	β-Galactosidase enzyme in trehalose	Bürki et al. (2011)
75–91	800	Hypromellose (enteric film coating and emulsifier)	Gu et al. (2015)
>90	n.a.	Sodium alginate (polysaccharide)	Blasi et al. (2010)
81–85	50–500	Sodium chloride NaCl	Li et al. (2010)
80	300	Resveratrol in poly(ε-caprolactone), sodium deoxycholate, and trehalose	Dimer, Ortiz, Pohlmann, and Guterres (2015)
50–78	10–50	Trehalose, mannitol or disodium phosphate surfactant, polysorbate	Schmid (2011) and Schmid et al. (2009, 2011)
68–76	–	Bovine serum albumin (protein)	Lee et al. (2011)
60–63	–	Chitosan (antibacterial activity)	Ngan et al. (2014)
53	–	Hydroxytyrosol-β-cyclodextrin	Malapert et al. (2019)

In general, the slow and gentle drying in a nano spray dryer yields spherical and compact particles. Small amounts of surface-active compounds (e.g., polysorbate) in the formulations are typically used to optimize the smoothness and sphericity of the particles, as shown by several researchers (Bürki et al., 2011; Li et al., 2010; Schmid, 2011; Schmid et al., 2009, 2011). Surfactants balance the surface-to-viscous forces inside the drying droplet and enable the formation of a smooth spherical surface on the dry particle (Moghbeli, Jafari, Maghsoudlou, & Dehnad, 2019). However, hollow, porous, and encapsulated structures with wrinkled, shriveled, or even doughnut-like shapes are also possible (Arpagaus et al., 2017).

After nano spray drying, the activity of the encapsulated product is preserved if the powder is stored under controlled conditions and if a stabilizer is added into the feed formulation. Most nano spray-dried powders are amorphous due to the short drying time, which is too short to form crystalline structures. To prevent recrystallization of amorphous drugs, the powders are stored under dry conditions. For example, Pérez-Masiá et al. (2015) observed bioactive stability of folic acid (vitamin B_9) in whey protein after 60 days under dry storage conditions and in darkness. Merchant et al. (2014) found no evidence of change in the crystallinity of chitosan powder after storage for 60 days at room temperature and ambient humidity. In addition, the nano spray drying process itself has a negligible or only a marginal impact on the product degradation or aggregation. Schmid (2011) detected a slight reduction in L-lactic dehydrogenase enzyme activity during pump circulation. Bürki et al. (2011) showed that nano spray-dried β-galactosidase enzyme in trehalose lost only 3% of its activity during 3 weeks of storage at 70°C. Optimized 600-nm-sized powder of α-amylase enzyme in sucrose retained 72% of its activity after 60 days (Abdel-Mageed et al., 2019). An option to minimize the potential of activity loss during the nano spray drying process is to cool the feed vessel in ice (Amsalem et al., 2017; Schoubben et al., 2013; Torge, Grützmacher, Mücklich, & Schneider, 2017) or to use a larger spray mesh to reduce the mechanical shear of atomization (Abdel-Mageed et al., 2019; Bürki et al., 2011).

Table 9 provides some data on encapsulation efficiency and loading of different bioactive food ingredients by nano spray drying. For example, Kyriakoudi and Tsimidou (2018) encapsulated aqueous saffron extracts in maltodextrin by nano spray drying. The encapsulation efficiency of the crocins was found to range between 54% and 81%. It was also found that the dried particles had a low moisture content of 3.3 to 3.9%.

Table 9 Encapsulation efficiencies and bioactive compound loadings achieved by nano spray drying (– = not available).

Bioactive compound	Wall material	Bioactive loading	Encapsulation efficiency	Reference
Folic acid (vitamin B_9)	Resistant starch	–	53%	Pérez-Masiá et al. (2015)
Folic acid (vitamin B_9)	Whey protein	–	84%	Pérez-Masiá et al. (2015)
Hydroxytyrosol (from olive oil)	β-Cyclodextrin	–	84 ± 3%	Malapert et al. (2019)
Resveratrol	Poly(ε-caprolactone, sodium deoxycholate, and trehalose	31%	–	Dimer, Ortiz, et al. (2015)
Saffron extracts (i.e., hydrophilic apocarotenoids crocins and picrocrocin)	Maltodextrin	1:5, 1:10, 1:20 core-wall ratio (w/w)	54%–81%	Kyriakoudi and Tsimidou (2018)

The size, shape, surface charge, wall composition, molecular weight, etc. play a major role on the release and bioavailability of bioactive food ingredients. The mathematical models for controlled release of substances are, for example, summarized by Estevinho, Rocha, Santos, and Alves (2013). The release of a bioactive compound in an ideal system may follow zero (constant release rate, pure material, and no encapsulation)-, half (matrix particles)-, or first (core is a solution)-order kinetics. The equations of Higuchi or Korsmeyer-Peppas are generally used to characterize the kinetic mechanism of controlled release of substances.

Commonly applied analytical methods to characterize the nano spray-dried powders are scanning electron microscopy (SEM) to determine particle size and morphology, laser diffraction to measure particle size (dynamic light scattering, DLS), and X-ray diffraction (XRD) or differential scanning calorimetry (DSC) to identify the amorphous/crystalline state.

3 Food and nutraceutical applications

Since its market launch in 2009, the Nano Spray Dryer B-90 has been used in the laboratory primarily in pharmaceutical research (Arpagaus, 2011,

2012, 2018b, 2018c). The use of nano spray drying for the nanoencapsulation of bioactive food ingredients is still at an early stage but is constantly evolving (Anandharamakrishnan & Ishwarya, 2015a; Assadpour & Jafari, 2019). This section presents published works on bioactive food applications performed with a nano spray dryer, along with a brief overview of the results obtained.

3.1 Polymeric wall materials

A number of research studies have demonstrated the ability of nano spray drying to produce submicron powders from polymeric wall materials. Table 10 shows experimental conditions that can be used as a first guide for the application of a Nano Spray Dryer B-90 with similar substances. Fig. 12 shows several SEM images of representative nano spray-dried polymeric wall materials.

Table 10 Process conditions for nano spray drying of polymeric wall materials for food applications.

Polymeric wall material	*T* in (°C)	*T* out (°C)	Drying gas (L/min)	Particle size (μm)	Reference
Gum arabic, whey protein, maltodextrin (DE 12), polyvinyl alcohol, and modified starch	100	38–60	100	0.2–1.1	Li et al. (2010)
Gum arabic (1%)	120	50–60	130	0.8–3.7	Oliveira et al. (2013)
Gum arabic (1%)	80–100	54–65	133	0.4–2.5	Büchi Labortechnik AG (2009)
Sodium alginate	110	50	100	0.4–1.2	Blasi et al. (2010)
Sodium alginate (0.1%)	120	50–60	130	0.8–5.5	Oliveira et al. (2013)
Sodium alginate/pectin	90	45	100	0.3–1.0	De Cicco et al. (2014)
Maltodextrin (DE 19) (1%)	100	33–39	120	0.5–2.1	Büchi Labortechnik AG (2017a)
Gelatine (1%)	80–90	44–50	133	0.3–2.0	Büchi Labortechnik AG (2009)
Trehalose (0.1% and 1%) with 0.05% polysorbate 20	60–100	30–45	115	0.3–5.0	Büchi Labortechnik AG (2009)

Continued

Table 10 Process conditions for nano spray drying of polymeric wall materials for food applications.—cont'd

Polymeric wall material	*T* in (°C)	*T* out (°C)	Drying gas (L/min)	Particle size (µm)	Reference
Trehalose, mannitol	60–100	30–45	115	0.3–3.0	Schmid (2011) and Schmid et al. (2009, 2011)
Leucine and trehalose	75	45	100	2.1–5.4	Feng et al. (2011)
Carboxymethyl cellulose (0.1%)	120	50–60	130	1.0–3.7	Oliveira et al. (2013)
Mannitol (1%)	80–90	40–50	133	0.4–2.0	Büchi Labortechnik AG (2009)
Nanosuspension of mannitol and poly(lactic-*co*-glycolic acid) (PLGA)	80	32–39	140	1.1–7.2	Torge et al. (2017)
Chitosan (30,000 Mv) in 1% acetic acid	120	55	130	0.6–1.6	Gautier et al. (2010)
Chitosan (low-density, 267–1200 cP) in 0.5% acetic acid	120	80	130	0.1–0.3	Ngan et al. (2014)
Chitosan/Tween 20 in 1% acetic acid	80–120	n.a.	100–150	0.3	O'Toole et al. (2012)
Bovine serum albumin with surfactant, polyoxyethylene, sorbitan monooleate	80–120	36–55	150 (N_2)	0.5–2.6	Lee et al. (2011)
Bovine serum albumin, 0.1% with 0.05% Tween 80	100	51–61	150	0.1–2.0	Büchi Labortechnik AG (2017b)

The comparison of the morphologies reveals that the primary particles are almost spherical in shape and that the most part is submicron in size. The wall materials used for the encapsulation of bioactive food ingredients by nano spray drying are mainly water-soluble polymers such as sodium alginate (Blasi et al., 2010; De Cicco et al., 2014; Oliveira et al., 2013), gum arabic (Büchi Labortechnik AG, 2017a; Li et al., 2010; Li, Anton, & Vandamme, 2015; Oliveira et al., 2013), gelatine (Büchi Labortechnik AG, 2009), whey protein (Li et al., 2010, 2015), polyvinyl alcohol (Li et al., 2010), modified starch (Li et al., 2010), and maltodextrin (Büchi Labortechnik AG, 2009, 2017a; Li et al., 2010).

Maltodextrins of various dextrose equivalents (DE) are typically used as carriers for flavors, fragrances and oils. Low-viscosity sodium alginate derived from marine algae is widely used as an emulsifier and immobilizer in food formulations. Gelatine is a tasteless animal protein and is often used as

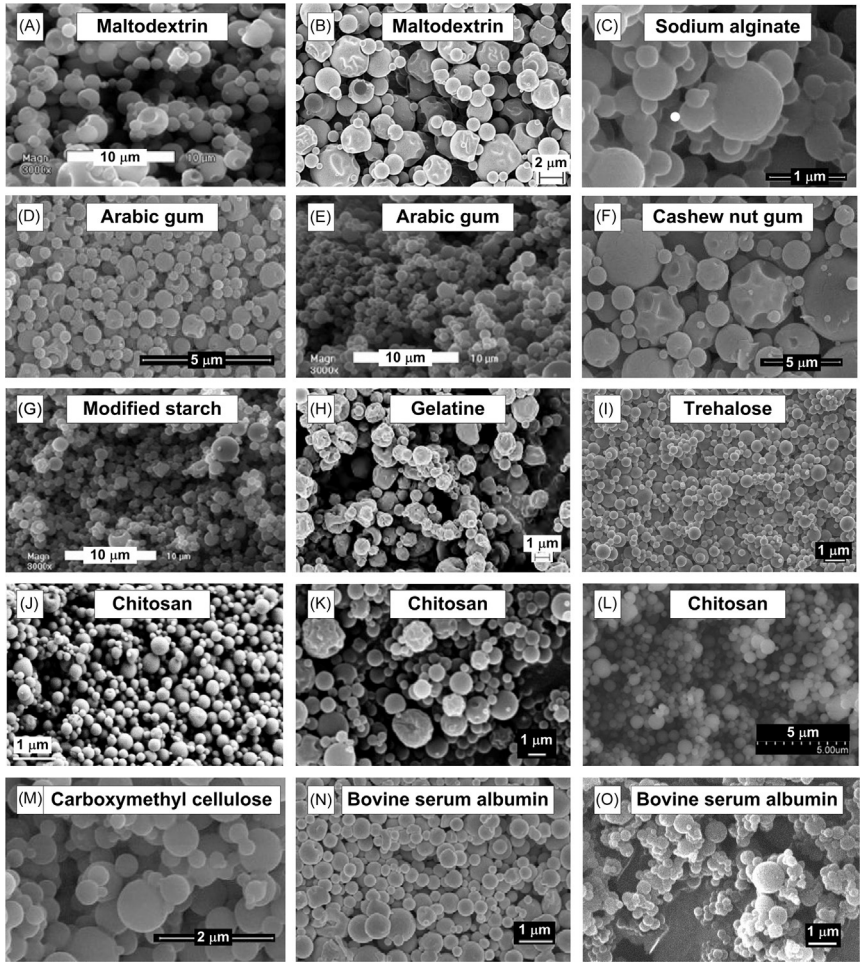

Fig. 12 SEM pictures of nano spray-dried particles obtained with the Nano Spray Dryer B-90. (A) Maltodextrin (DE 12), 1% (w/v) aqueous solution (Li et al., 2010), (B) maltodextrin (DE 19), 1% (Büchi Labortechnik AG, 2009), (C) sodium alginate, 0.1% (Oliveira et al., 2013), (D) gum arabic, 1% (Oliveira et al., 2013), (E) gum arabic, 1% (Li et al., 2010), (F) cashew nut gum, 1% (Oliveira et al., 2013), (G) modified starch, 1% (Li et al., 2010), (H) gelatine, 1% (Büchi Labortechnik AG, 2009), (I) trehalose, 1% with 0.05% polysorbate 20 (Tween 20) (Büchi Labortechnik AG, 2009), (J) chitosan, 0.025% in 1% acetic acid (O'Toole et al., 2012), (K) chitosan, 0.1% in 1% acetic acid (Gautier et al., 2010), (L) chitosan (276 cP), 0.1% in 0.5% acetic acid (Ngan et al., 2014), (M) carboxymethyl cellulose, 1% (Oliveira et al., 2013), (N) bovine serum albumin, 0.1% with 0.05% Tween 80 (Lee et al., 2011), (O) bovine serum albumin, 0.1% with 0.05% Tween 80 (Büchi Labortechnik AG, 2017b). *(All images reprinted with permission.)*

a gelling agent and for encapsulation in food. Mannitol (Torge et al., 2017), chitosan (Gautier et al., 2010; Ngan et al., 2014; O'Toole et al., 2012), leucine (Feng et al., 2011), and trehalose (Schmid, 2011; Schmid et al., 2009, 2011; Vereman, Thysens, Derdelinckx, Van Impe, & Van de Voorde, 2019) are also used as food encapsulating agents due to their high aqueous solubility and low toxicity. Trehalose is applied as a protein stabilizer increasing shelf life (Schmid et al., 2009; Vereman et al., 2019). Leucine is an amino acid and a useful dispersing agent (Feng et al., 2011). Chitosan offers advantages for mucosal delivery, such as low toxicity, good biodegradability, and antibacterial activity (Cerchiara et al., 2015; Dimer, de Souza Carvalho-Wodarz, Haupenthal, Hartmann, & Lehr, 2015; Merchant et al., 2014; Ngan et al., 2014; Nguyen, Nguyen, Wang, Vo, & Nguyen, 2017; Rampino, Borgogna, Blasi, Bellich, & Cesàro, 2013). Moreover, nano spray-dried chitosan particles strongly inhibited bacterial growth and have much potential as fat blocker (Gautier et al., 2010). Bovine serum albumin (BSA) is a protein derived from cows and has many applications in life science. It is often used as a model protein in numerous biochemical applications and in spray drying to evaluate the process as a heat-sensitive substance. Submicron particles are achieved with the 4.0-μm spray mesh at a BSA concentration of 0.1% (w/v) and a surfactant concentration of 0.05% (w/v) (Tween 80) (Arpagaus, 2012; Büchi Labortechnik AG, 2017b; Lee et al., 2011).

In general, a dilution of the solution leads to an end product with a smaller particle size. Typically, the solid concentrations are 0.1%–1% (w/v). Since a single encapsulating agent may not have all the ideal wall material properties, recent research has focused on mixtures of carbohydrates, gums, and proteins. There are many other common wall materials for encapsulation by spray drying (see Table 3), which shows in particular the potential for further applications in nano spray drying.

3.2 Water-soluble vitamins, polyphenols, and extracts

Vitamins are vital amines needed for the normal growth and function of the human body. However, vitamins are sensitive and unstable to exposure to high temperatures, oxygen, light, or moisture, which can lead to the loss of their functions (Katouzian & Jafari, 2016). Spray drying is the most common method for encapsulating vitamins. Vitamins are usually classified as fat soluble (vitamins A, D, E, and K) and water soluble (vitamins B and C). So far, there are a few studies on the encapsulation of water-soluble vitamins with nano spray drying (Oliveira et al., 2013; Pérez-Masiá et al., 2015). Table 11 lists the identified optimal experimental process parameters.

Table 11 Process conditions for nano spray drying of water-soluble vitamins, polyphenols, and extracts (– = not available).

Bioactive ingredient	Encapsulating wall material	Solvent, solid concentration	*T* in (°C)	*T* out (°C)	Drying gas (L/min)	Particle size (μm)	Reference
Vitamin B_{12}	Gum arabic, cashew nut gum, sodium alginate, carboxymethyl cellulose, Eudragit RS100	0.1%–1% (w/v) in water	120	50–60	130	0.2–5.5	Oliveira et al. (2013)
Folic acid (synthetic vitamin B_9)	Guar gum, whey protein, resistant starch	Water, 0.4% (w/v)	90	45	140	0.2–4.5	Pérez-Masiá et al. (2015)
Curcumin	Chitosan/Tween 20	Water with 1% acetic acid	80–120	–	100–150	0.3	O'Toole et al. (2012)
Curcumin	Human serum albumin	Water	120	–	150	0.2–0.7	Jain (2014)
Curcumin in nanogels	Egg yolk low-density lipoprotein (LDL), pectin, or carboxy-methyl cellulose (CMC)	Water	70–120	50–60	120	0.5–1.5	Zhou et al. (2018, 2016)
Curcumin	Structural change without wall material	Ethanol	65	–	120	0.4–1.3	Büchi Labortechnik AG (2017c)
Hydroxytyrosol (biophenol of olive oil)	β-Cyclodextrin (β-CD)	Water	100	–	100	0.4–3.2	Malapert et al. (2019)
Resveratrol	Poly(ε-caprolactone), sodium deoxycholate, trehalose	Water/acetone (50:50)	55	–	110 (N_2/CO_2)	1–5	Dimer, Ortiz, et al. (2015)
Guava leaf extracts	Aqueous extract	Water	105	38	–	–	Camarena-Tello et al. (2018)
Saffron extracts (apocarotenoids crocins and picrocrocin)	Maltodextrin	Water, 2.5% (w/w)	100	45–50	100	1.5 (mean)	Kyriakoudi and Tsimidou (2018)

In particular, Oliveira et al. (2013) encapsulated hydrophilic vitamin B_{12} in gum arabic, cashew nut gum, sodium alginate, and carboxymethyl cellulose. A deficiency of vitamin B_{12} can be associated with coronary artery disease. The influence of the different polymer properties was evaluated in terms of controlled release performance. Aqueous solutions with a viscosity of 6.3–9.2 mPa s were successfully atomized with the vibrating mesh technology of the Nano Spray Dryer B-90. SEM micrographs displayed spherical submicron particles. The reduction of the particles size and the increase of the specific surface area contributed to speed up the release rate kinetics.

More recently, Pérez-Masiá et al. (2015) encapsulated water-soluble folic acid (synthetic vitamin B_9) in whey protein and resistant starch through nano spray drying. Folic acid has important roles in cell metabolism and can be obtained in its natural form (folate) by consuming green vegetables or dietary supplements (Oprea & Grumezescu, 2017). Specific dosages of folic acid are needed in the daily diet during phases of cell division and growth such as pregnancy and infancy. By nano spray drying, spherical submicron and micron capsules were obtained. Whey protein–based capsules achieved an encapsulation efficiency of about 84%, compared with about 53% with resistant starch, which was attributed to the different interactions between the bioactive and the protein matrix. It was further observed that whey protein conserved the folic acid better against degradation during storage in an aqueous solution as well as dry storage. The capsules made of whey protein were able to keep the bioactive stability at almost 100% in darkness and under dry storage conditions after 60 days.

A number of research studies have shown that nano spray drying can be used as an appropriate method for the nanoencapsulation of phenolic compounds and antioxidants (Büchi Labortechnik AG, 2017c; Camarena-Tello et al., 2018; Dimer, Ortiz, et al., 2015; Jain, 2014; Malapert et al., 2019; O'Toole et al., 2012; Zhou et al., 2018; Zhou, Wang, Hu, & Luo, 2016). The optimized process conditions and the obtained particle sizes are summarized in Table 11. Polyphenols are found naturally in fruits and vegetables and primarily consist of flavonoids and nonflavonoid polyphenolics (Faridi Esfanjani, Assadpour, & Jafari, 2018). The antioxidant properties prevent degenerative diseases such as cancer, inflammation, and neurodegenerative diseases (Faridi Esfanjani & Jafari, 2016).

Curcumin is a polyphenolic compound derived from the rhizome of the turmeric plant *Curcuma longa* L. Its therapeutic potential as an antioxidant, antiinflammatory, antimutagenic, and anticancer agent is limited by poor uptake in the body due to its insolubility in water, rapid metabolism by

the intestinal mucosa and liver, and quick excretion. Specific delivery vehicles are used to enhance the bioavailability of curcumin (Rafiee, Nejatian, Daeihamed, & Jafari, 2019).

O'Toole et al. (2012) encapsulated curcumin in in chitosan/Tween 20 via nano spray drying. Chitosan offers improved mucous adhesiveness, nontoxicity, biocompatibility, and biodegradability. Spherical particles with 285 ± 30-nm diameter were produced. Release studies in 1% acetic acid and buffer solution revealed nearly 40% of curcumin release in the first 5 min of the experiment. All detectable curcumin release was complete within 2 h. Jain (2014) encapsulated curcumin in cross-linked human serum albumin. The particles were smooth, spherical, and submicron-sized in a range of 0.2–0.7 μm. The cross-linked albumin implied a slower release of curcumin and the data followed a first-order release profile.

In an application note of Büchi Labortechnik AG (2017c), curcumin particles of 367 to 1290 nm could be obtained directly from a 0.1% (w/w) curcumin solution prepared in ethanol. The structural change of the curcumin powder was established by operating a Nano Spray Dryer B-90 HP in closed loop configuration using an Inert Loop B-295 and inert gas N_2/CO_2. The gas flow rate was set up between 120 and 150 L/min, the inlet temperature of 65°C, and the spray rate at 80%. SEM images of nano spray-dried curcumin powder showed a spherical morphology, while the original curcumin had a needle-like morphology in the 100-μm scale (see Fig. 13).

Dimer, Ortiz, et al. (2015) encapsulated resveratrol, a polyphenol derived, for example, from grapes, with antioxidant properties, in poly(ε-caprolactone), sodium deoxycholate, and trehalose. Most particles were in the size range of 1–5 μm and showed a great potential for the treatment

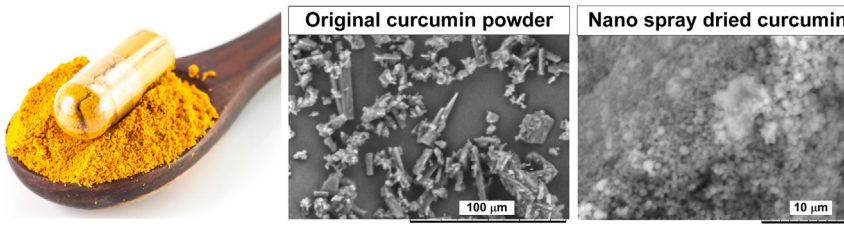

Fig. 13 (Left & middle) Original curcumin powder and (right) after nano spray drying as 0.1% (w/w) ethanol solution, illustrating the structural nanoionization of a pure bioactive substance (Büchi Labortechnik AG, 2017c).

of pulmonary arterial hypertension. The nano spray drying process provided high yields of approximately 80% with low moisture content <2%. The in vitro release of resveratrol was sustained for up to 12 h. After 30 min, 25% of the resveratrol was released.

As an example for the encapsulation of plant extracts, Kyriakoudi and Tsimidou (2018) encapsulated aqueous saffron extracts (i.e., hydrophilic apocarotenoids crocins and picrocrocin) in maltodextrin by nano spray drying. Spherical particles with smooth surfaces (mean particle size 1.5 μm) were obtained using a 4-μm spray mesh. The product yield was found to be 71% to 87%, the encapsulation efficiency of the crocins in a range between about 54% and 81%. The particles were found to have low moisture content of 3.3% to 3.9%. The nanoencapsulation resulted in increased stability of crocins and picrocrocin under thermal and gastrointestinal (GI) conditions. As another example, Camarena-Tello et al. (2018) nano spray-dried the aqueous extract of guava leaves and quantified the total polyphenols and flavonoids contents and the in vitro ability to scavenge hydroxyl radicals.

Malapert et al. (2019) encapsulated hydroxytyrosol (HT) into β-cyclodextrin (β-CD) by nano spray drying. HT is found in olive oil and leaves and is used as a functional food additive or ingredient to protect blood fats from oxidative damage. Cyclodextrins (e.g., natural cyclic oligosaccharides from the degradation of starch) offer a hydrophobic cavity and can accommodate guest compounds to form inclusion complexes, while their hydrophilic outer surface provides water solubility. An equimolar aqueous solution of HT and β-CD (final concentration of 5 mM each) was prepared and filtered before spray drying. Spherical particles from 0.4 to 3.4 μm were formed by nano spray drying while freeze-drying only provided irregular shapes. An encapsulation efficiency of 84% and a final moisture content of 7% were obtained.

Nano spray drying has also been utilized as a process to dry formulated nanoparticles containing bioactive food compounds, namely, nanoemulsions (Büchi Labortechnik AG, 2017a; Hu, Gerhard, Upadhyaya, Venkitanarayanan, & Luo, 2016; Li et al., 2010, 2015; Prasad Reddy, Padma Ishwarya, & Anandharamakrishnan, 2019; Veneranda et al., 2018; Wang, Soyama, & Luo, 2016), nanogels (Zhou et al., 2018, 2016), and solid lipid nanoparticles (SLNs) (Wang, Bae, Lee, & Luo, 2018; Wang, Hu, Zhou, Xia, et al., 2016; Wang, Hu, Zhou, Xue, & Luo, 2016; Wang, Ma, Lei, and Luo, 2016; Wang et al., 2017; Xue, Wang, Hu, Zhou, & Luo, 2017, 2018). In most cases, the formulated nanoparticles are mixed with additional excipients and dispersing

agents prior to nano spray drying to fabricate fine powders. Further details on the applications and process conditions are given in the following sections.

3.3 Nanoemulsions with lipophilic bioactive compounds

Nanoemulsions are particularly suitable for solubilization of lipophilic bioactive compounds, such as essential oils in aqueous phase. Essential oils are derived from a variety of natural sources like vegetables, herbs, and fruits and contain bioactive compounds with well-known antioxidant and antimicrobial activities. The main challenges are their poor water solubility and high volatility (Veneranda et al., 2018). Using nanoemulsions in food applications offers the potential to increase the absorption rate, improve bioavailability, enable target delivery, and so forth. Thereby, surfactants and emulsifiers play a decisive role in the production of nanoscale oil droplets by lowering the interfacial tension between the aqueous and oil phases.

In the food industry, nanoemulsions from essential oils are typically prepared by high-energy methods such as high-pressure homogenization, ultrasonication, and microfluidization (Büchi Labortechnik AG, 2017a; Hu et al., 2016; Jafari et al., 2015; Quintanilla-Carvajal et al., 2010; Wang, Soyama, et al., 2016) or low-energy methods like self-emulsification (Jafari et al., 2015; Jafari, Paximada, et al., 2017; Li et al., 2010, 2015; Veneranda et al., 2018). Fig. 14 schematically illustrates the manufacturing processes of various oil nanoemulsions prior to nano spray drying.

Table 12 summarizes the experimental process parameters of published studies on nano spray drying for the encapsulation of nanoemulsions (Büchi Labortechnik AG, 2017a; Hu et al., 2016; Li et al., 2010, 2015; Prasad Reddy et al., 2019; Veneranda et al., 2018; Wang, Soyama, et al., 2016). Fig. 15 shows some SEM images of the resulting nano spray dried powders containing nanoemulsions.

In particular, Li et al. (2010, 2015) encapsulated oil-in-water nanoemulsions of vitamin E acetate (oil droplets below 100 nm) in gum arabic, modified starch, maltodextrin, and whey protein (1 w% wall material) (Fig. 14A). Vitamin E acetate was chosen as a model for the oily phase. Vitamin E is an antioxidant that can scavenge free radicals and is also involved in immune function (Oprea & Grumezescu, 2017). The nanoemulsions were obtained spontaneously by low-energy emulsification after mixing the two phases with 1% (w/v) aqueous wall material solutions in a weight ratio of 1:4. A surfactant immediately stabilized the formed nanodrops (Li et al., 2015). Optimal drying conditions of 100°C inlet

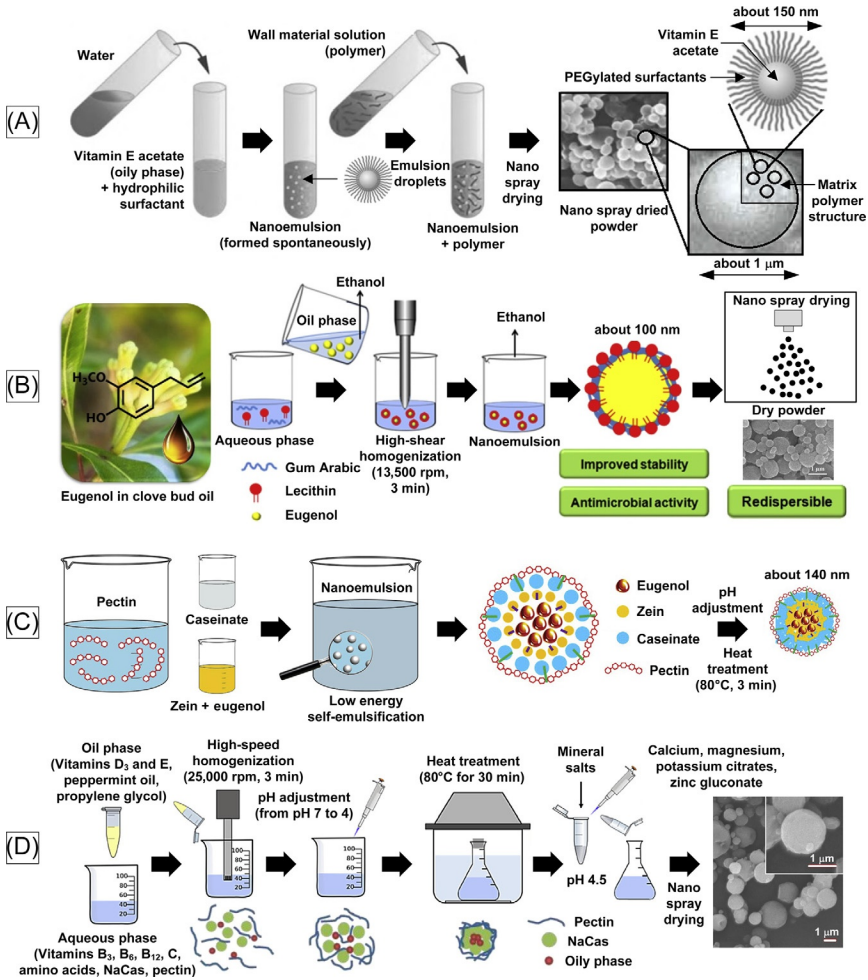

Fig. 14 Preparation procedures of (A) spontaneously formed vitamin E oil-in-water nanoemulsion <100 nm in whey protein (Li et al., 2010, 2015), (B) antimicrobial eugenol oil nanoemulsion with gum arabic and lecithin (Hu et al., 2016), (C) eugenol-loaded pectin/NaCas/zein nanoparticles by a pH- and heat-induced complexation process (Veneranda et al., 2018), and (D) functional drink containing fat- and water-soluble nutrients (Wang, Soyama, et al., 2016).

temperature and 40–60°C outlet temperature ensured no damage of the food ingredients during nano spray drying. Submicron solid particles (460–730-nm distributions) were produced with almost 100% encapsulation efficiency (Fig. 15A and B). Redissolving the spray-dried nanoparticles in water led to nanoemulsions without any significant degradation or size

Table 12 Process parameters of published studies on nano spray-dried nanoemulsions (– = not available).

Bioactive substance, application	Encapsulating wall material	Solvent	*T* in (°C)	*T* out (°C)	Drying gas (L/min)	Dried particle size (μm)	Reference
Vitamin E acetate oil-in-water (vitamin supplement)	Whey protein, gum arabic, modified starch, maltodextrin	Water	100	38–60	100	0.4–1.1	Li et al. (2010, 2015)
Eugenol oil (antimicrobial)	Gum arabic, lecithin	Water, ethanol	100	–	100–110	0.2–0.5	Hu et al. (2016)
Eugenol oil (antimicrobial)	Zein, sodium caseinate (NaCas), pectin	Water	100	–	120	1.0–1.5	Veneranda et al. (2018)
Functional drink as the nanoemulsion of antimicrobial peppermint oil, vitamins (D3, E, B3, B6, B12, and C), minerals, amino acids	NaCas, pectin, propylene glycol	Water	100	–	120	1–2	Wang, Soyama, et al. (2016)
Sunflower oil	Maltodextrin (DE 19), Tween 20	Water	120	45	100	1.0–2.5	Büchi Labortechnik AG (2017a)
Omega-3 fatty acids	Lactoferrin	Water	80	40–46	–	0.8–3 (agglomerated)	Nunes et al. (2018)
Coffee bean oil	Whey protein, Tween 80	Water	90	45	90–110	0.2–0.4	Prasad Reddy et al. (2019)

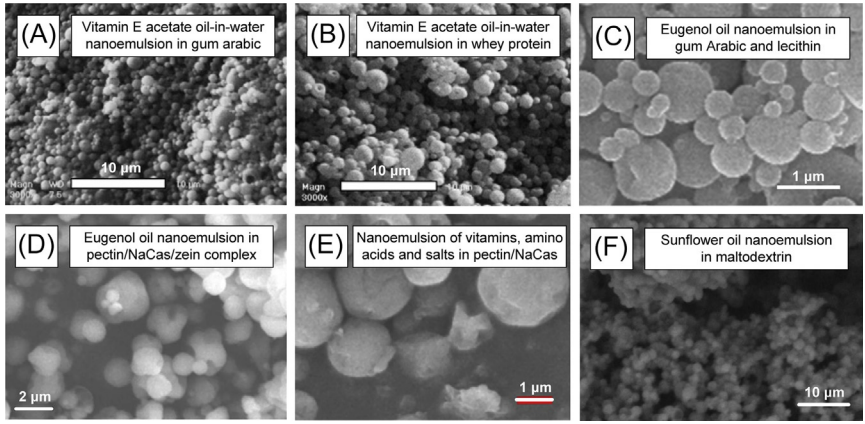

Fig. 15 Nano spray-dried powders obtained from (A) vitamin E oil-in-water nanoemulsion in gum arabic (Li et al., 2010) and (B) in whey protein (Li et al., 2010); (C) eugenol oil nanoemulsion in gum arabic and lecithin (Hu et al., 2016); (D) eugenol oil nanoemulsion in pectin/NaCas/zein complex (Veneranda et al., 2018); (E) oil- and water-soluble vitamins, amino acids, and mineral salts as functional drink (Wang, Soyama, et al., 2016); (F) sunflower oil emulsion in maltodextrin (1%, w/v) (Büchi Labortechnik AG, 2017a).

increase (Li et al., 2010, 2015). Overall, the nano spray drying technology was able to encapsulate nanoemulsions smaller than 100 nm (an order of magnitude smaller than the sprayed droplets) into separated solid particles and to preserve the integrity of the nanoemulsion system.

Hu et al. (2016) and Veneranda et al. (2018) prepared eugenol oil-loaded nanoemulsions with enhanced antimicrobial activity (i.e., inhibiting bacterial growth), good physical stability, and excellent redispersibility after nano spray drying (Fig. 14B and C). Eugenol is a naturally occurring essential oil extracted from cloves and is known for its strong bactericidal and antioxidant properties, which is seen as promising to be applied in the food industry as a food preservative. Gum arabic and lecithin were used as food-grade natural emulsifiers (ratio of 4:1 w/w), and nanoemulsions of around 100 nm were obtained by high-speed homogenization at 13,500 rpm for 3 min. The addition of ethanol as a cosurfactant to the eugenoil oil improved the morphology and homogeneity of the powders during nano spray drying. Spherical powders in the range of 200 to 500 nm with smooth surface could be produced (Fig. 15C), which exhibited excellent redispersibility in water. The eugenol oil droplets were well surrounded and trapped by lecithin and gum arabic. The powders were about 20 to 50 times smaller than those dried by conventional spray dryers (i.e., usually 10 to 25 µm).

Veneranda et al. (2018) prepared about 140-nm-sized nanoemulsions by a pH- and heat-induced self-emulsification method (80°C for 60 min) using food polymers zein, sodium caseinate (NaCas), and pectin. Zein is derived from corn and is a suitable storage protein for liquid-liquid dispersions due to its unique solubility. Caseinate and pectin are known for their pH- and heating-induced electrostatic interactions. Stable eugenol-loaded biopolymeric complex nanoparticles could be prepared by premixing eugenol with zein and then complexing among the biopolymers caseinate and pectin. The colloidal eugenol-loaded complex nanoparticles were nano spray-dried and transformed to fine 1 to 1.5-μm-sized powders (Fig. 15D) enabling a long-term storage in powder form with exceptional microbial stability (i.e., no growth of bacteria up to 2 months), a fast redispersion capability, and thus a greater potential to the applications in food industry.

Wang, Soyama, et al. (2016) developed a novel nanoemulsion-based functional drink from all natural food ingredients using casein/pectin nanocomplex particles as a delivery system (Fig. 14D). Nano spray drying was applied to form instant powders to improve the shelf life and transportation. This property also gains a ready-to-drink character by dissolving them in water, milk, or coffee. The functional drink consisted of both lipophilic (vitamin D_3 and E) and hydrophilic vitamins (B_3, B_6, B_{12}, and C), mineral salts (i.e., calcium citrate, magnesium citrate, potassium citrate, and zinc gluconate), and amino acids, as well as antimicrobial peppermint oil dissolved in propylene glycol. All water-soluble vitamins and the amino acid were completely dissolved in pectin solution. Pectin from citrus peel is a naturally occurring polysaccharide with excellent gelling properties and can stabilize casein micelles. The oil phase was first homogenized at high speed (25,000 rpm for 3 min) into aqueous phase with NaCas from bovine milk as natural emulsifier to obtain a nanoemulsion. Then, the pH value of the nanoemulsion was reduced by the addition of citric acids drops, followed by a thermal treatment at 80°C for 30 min to form complex nanoparticles (Luo, Pan, & Zhong, 2015). The final samples were either freeze-dried or nano spray-dried to produce dry powders of the prepared functional drink. The freeze-dried powders exhibited a flake-like morphology, while the nano spray-dried powders were spherical particles of about 1 to 2 μm size (Fig. 15E). A higher concentration of biopolymeric NaCas/pectin matrix was beneficial to obtain a better morphology of the dry powders.

Transparent sunflower oil emulsions of about 100 nm were also encapsulated in maltodextrin (Büchi Labortechnik AG, 2017b). Eight grams of maltodextrin (DE 19) was dissolved in 80-mL deionized water, and

12-mL sunflower oil was added and high shear homogenized with 8-mL Tween 20 surfactant. Particles with 1.0–2.56 μm size (Fig. 15F) with a recovery yield of approx. Ninety percent of 45-mg sample quantities were obtained using a Nano Spray Dryer B-90 HP. The optimized process parameters were 5.0 μm spray mesh size, 120 L/min drying air flow, and 100°C inlet temperature.

Nunes, Bourbon, Martins, Pastrana, and Vicente (2018) developed nanoemulsions of omega-3 (ω-3) fatty acids with water-soluble lactoferrin as a natural emulsifier and dried the nanoemulsions in a Nano Spray Dryer B-90 HP with a small nebulizer. Omega-3 (ω-3) fatty acids offer health benefits, such as the reduction of cardiovascular disease. The inlet temperature of the spray drier was kept constant at 80°C, and the outlet temperature varied between 40°C and 46°C. The nanoemulsions were produced by high-pressure homogenization (five cycles, 20,000 psi) with 2% (w/w) lactoferrin and 5% (w/w) ω-3 fatty acids. Transmission electron microscopy (TEM) images showed an average nanoemulsion size of about 170 nm. Nano spray drying produced particle aggregates of about 0.8 to 3-μm-sized primary particles. The ω-3 fatty acids were successfully encapsulated. The slow release of the ω-3 fatty acids under different simulated gastrointestinal conditions (e.g., 20% ethanol) is promising for potential incorporation in foods with lipophilic character such as ice cream and mayonnaise.

Recently, Prasad Reddy et al. (2019) reported on the nanoencapsulation of roasted coffee bean oil in whey protein by nano spray drying. The powders showed a smooth and spherical particle morphology with a mean particle size of about 305 ± 100 nm and a homogeneous size distribution. The coffee oil emulsions were formed with a rotor-stator homogenizer operated at 20,000 rpm for 5 min. First, an aqueous wall material solution (0.4%, w/v) was prepared; then, roasted coffee oil and Tween 80 (emulsifier) were added at 3% (w/w) and 5% (w/w), respectively. The viscosity was about 0.9 mPa s. The results were considered promising for the food ingredient and flavor industries to increase the oxidative stability of coffee oil and facilitate controlled release of hydrophobic flavor compounds.

3.4 Nanogels made of egg yolk low-density lipoprotein

Nanogels made of egg yolk low-density lipoprotein (LDL) and polysaccharides are also investigated as nutrient delivery systems with promising encapsulation and release potentials. Zhou et al. (2016) reported a pH- and

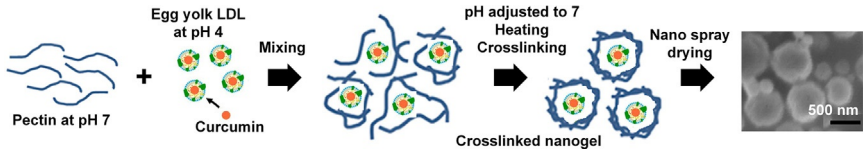

Fig. 16 Schematic illustration of the formulation of egg yolk low-density lipoprotein (LDL)/pectin nanogels. *(Based on Zhou, M., Khen, K., Wang, T., Hu, Q., Xue, J., Luo, Y. (2018). Chemical crosslinking improves the gastrointestinal stability and enhances nutrient delivery potentials of egg yolk LDL/polysaccharide nanogels.* Food Chemistry, 239, *840–847; Zhou, M., Wang, T., Hu, Q., Luo, Y. (2016). Low density lipoprotein/pectin complex nanogels as potential oral delivery vehicles for curcumin.* Food Hydrocolloids, 57, *20–29).*

heat-induced method for the fabrication of such nanogels with a diameter of only 58 nm. The nano spray-dried powders produced from the nanogels exhibited an average particle size of about 1 μm and could be redispersed in water while maintaining their size in the nanoscale. Encapsulation of curcumin, as a model nutrient, into the nanogels was effectively achieved. Fig. 16 illustrates the encapsulation procedure of curcumin in nanogels. Curcumin was first dissolved in ethanol at 2 mg/mL and then added to LDL solutions to reach a curcumin/LDL ratio of 1%. The encapsulated curcumin in the nanogels showed a pH-dependent controlled release profile in simulated acidic gastrointestinal (GI) conditions (pH 2, 4, and 7.5) compared with free curcumin, demonstrating as potential oral delivery vehicles for lipophilic nutrients. The extreme acidic conditions in the human stomach are still a major challenge for further application of egg yolk LDL–based nanogels.

To improve the GI stability, Zhou et al. (2018) chemically cross-linked protein–pectin and protein–carboxymethyl cellulose nanogels by 1-ethyl-3-(3-dimethylaminopropyl) and carbodiimide/*N*-hydroxysuccinimide. Compared with original un-cross-linked nanogels, cross-linking significantly enhanced the resistance against biodegradation by digestive enzymes and aggregation under acidic pH conditions. Moreover, curcumin exhibited a sustained release profile in simulated GI fluids compared with noncross-linked nanogels. The encapsulation efficiency was about 80%, and the particle size and morphology of the nanogels did not change due to cross-linking.

3.5 Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are regarded as promising nanoscale delivery systems for the encapsulation of lipophilic bioactives to enhance their stability and improve their bioavailability in foods. SLNs offer a high loading

capacity in their lipid core compared with other colloidal delivery systems. Several studies have shown that SLNs can be successfully encapsulated using nano spray drying technology (Wang et al., 2018, 2017; Wang, Hu, Zhou, Xia, et al., 2016; Wang, Hu, Zhou, Xue, et al., 2016; Wang, Ma, et al., 2016; Xue et al., 2017, 2018). Table 13 summarizes possible material combinations for nano spray drying of SLNs.

Wang et al. (2018, 2017) recently developed a new oral delivery platform for lipophilic bioactives from all-natural biomaterials, that is, solid lipid–polymer hybrid nanoparticles (SLPNs), consisting of SLNs as the inner core, bovine serum albumin (BSA)–dextran (BD) Maillard conjugate as natural emulsifier, and pectin as secondary polymeric coating. Fig. 17 shows a schematic diagram of the fabrication process.

Table 13 Process conditions for nano spray drying of solid lipid nanoparticles (SLNs), 100°C/50°C[a] inlet/outlet drying temperature, 120 L/min drying gas flow rate, and water as solvent.

Bioactive substance	Encapsulation wall material	Particle size (μm)	Reference
Curcumin-loaded solid lipid nanoparticles (SLNs)	Stearic acid, sodium caseinate (NaCas) (emulsifier), pectin (stabilizer)	0.5–1.0	Xue et al. (2017, 2018)
Curcumin-loaded SLNs (layer by layer coated)	Compritol ATO 888 (glyceryl behenate), NaCas, pectin	0.5–1.0 3–5	Wang, Hu, Zhou, Xia, et al. (2016) and Wang, Ma, et al. (2016)
Polysaccharide-coated SLNs	Pectin, gum arabic, alginate, CMC	1–10	Wang, Hu, Zhou, Xue, et al. (2016)
Curcumin loaded in caseinate-zein-polysaccharide complex nanoparticles	Zein, caseinate, pectin	1–4	Chang et al. (2017)
Curcumin in solid lipid–polymer hybrid nanoparticles (SLPNs) (SLNs as core and BSA-dextran Maillard conjugate/pectin as shell)	Bovine serum albumin (BSA), dextran, pectin (secondary polymeric coating)	1–1.5	Wang et al. (2018)

[a]Extrapolated from Fig. 11.

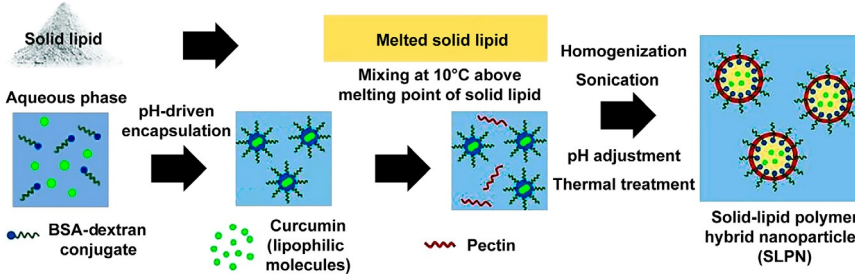

Fig. 17 Schematic diagram of fabrication of pectin-coated and curcumin-encapsulated solid lipid–polymer hybrid nanoparticles (SLPNs). *(Based on Wang, T., Bae, M., Lee, J., Luo, Y. (2018). Solid lipid-polymer hybrid nanoparticles prepared with natural biomaterials: a new platform for oral delivery of lipophilic bioactives.* Food Hydrocolloids, 84*, 581–592).*

Two glyceride lipids (i.e., Compritol 888 ATO and Precirol ATO 5) and four saturated fatty acids (i.e., behenic acid, stearic acid, palmitic acid, and myristic acid) were tested together with curcumin as a model lipophilic bioactive. Briefly, the SLPNs were prepared by emulsifying various solid lipids using homogenization and sonication techniques. Pectin solution was mixed with BD solution to form an aqueous phase. Then, the melted solid lipid was added into the aqueous phase under homogenization followed by sonication and cooling down in an ice bath to recrystallize the solid lipid core. The pH of the BD solutions was first adjusted to pH = 12 to encapsulate curcumin powder, followed by stirring, and neutralizing to pH = 7. The colloidal SLPN samples were then spray-dried in a Nano Spray Dryer B-90 under following operating conditions: 100°C inlet temperature, 120 L/min drying gas flow rate, and 5.5 μm spray mesh size (Wang et al., 2018, 2017). The produced nano spray-dried powders were in the range of 1 to 1.5 μm and showed excellent stability and redispersibility in water, as shown in Fig. 18.

Although the original size of the SLPN particles of about 250 nm was slightly increased in the spray-dried powders, they were able to reassemble their colloidal nanostructures when redispersed in water. The encapsulation efficiency of curcumin in the various solid lipids was in the range of 39% and 82%. SLPNs prepared with glyceryl lipids (ATO 888 and ATO 5) exhibited a higher encapsulation efficiency than fatty acids groups, which was attributed to the higher hydrophobicity of the longer hydrocarbon chains leading to higher accommodation of lipophilic payload. The in vitro release profiles of curcumin from SLPNs under GI environment (pH = 2 and pH = 7) after 6 h incubation were about 40% to 56% compared with the free curcumin control.

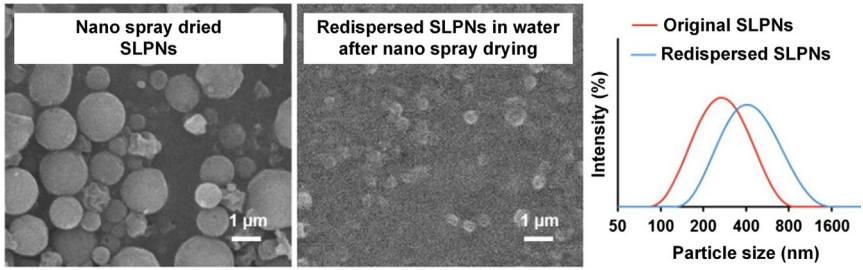

Fig. 18 Characterization of nano spray-dried and water-redispersed solid lipid–polymer hybrid nanoparticles (SLPNs) made of dissolved Compritol 888 ATO, BSA-dextran conjugate, and pectin. The particle size distribution was measured by dynamic light scattering. *(Data from Wang, T., Xue, J., Hu, Q., Zhou, M., Chang, C., Luo, Y. (2017). Synthetic surfactant- and cross-linker-free preparation of highly stable lipid-polymer hybrid nanoparticles as potential oral delivery vehicles.* Scientific Reports*, 7, 2750).*

In previous studies, the feasibility of nano spray drying to transform caseinate/lecithin- and polysaccharide-coated colloidal SLNs and nanostructured lipid carriers (NLCs) to fine powders was demonstrated by Wang, Hu, Zhou, Xia, et al. (2016) and Wang, Hu, Zhou, Xue, et al. (2016) (Fig. 19).

Wang, Hu, Zhou, Xia, et al. (2016) prepared "all natural" layer-by-layer redispersible SLNs by nano spray drying. The SLNs were made of Compritol 888 ATO (glyceryl behenate) and NaCas and coated with pectin. Wang, Hu, Zhou, Xue, et al. (2016) coated SLNs made from Compritol 888 ATO with various natural polysaccharides (i.e., pectin, gum arabic, alginate, carboxymethyl cellulose (CMC), and carrageenan) together with lecithin by nano spray drying. Among the five polysaccharides, carrageenan exhibited the best effect on producing small, spherical, and well-separated powders, followed by pectin, alginate, CMC, and gum arabic.

Wang, Ma, et al. (2016) further tested the feasibility of cross-linking the polymeric double layer made of NaCas and pectin for oral delivery of curcumin. The cross-linking significantly improved the physicochemical properties of the SLNs, resulting in a higher encapsulation efficiency and loading capacity, better stability, and slower release profile in simulated GI conditions. The cross-linking further helped forming homogenous nano spray-dried powders of 0.5 to 1 µm size. Overall, the biopolymer coatings played a critical role in producing spherical and uniform dry particles that were redispersible in water (Wang, Hu, Zhou, Xia, et al., 2016; Wang, Hu, Zhou, Xue, et al., 2016; Wang, Ma, et al., 2016). Optimal pH conditions (pH = 5) and thermal treatment (80°C for 30 min) were identified as

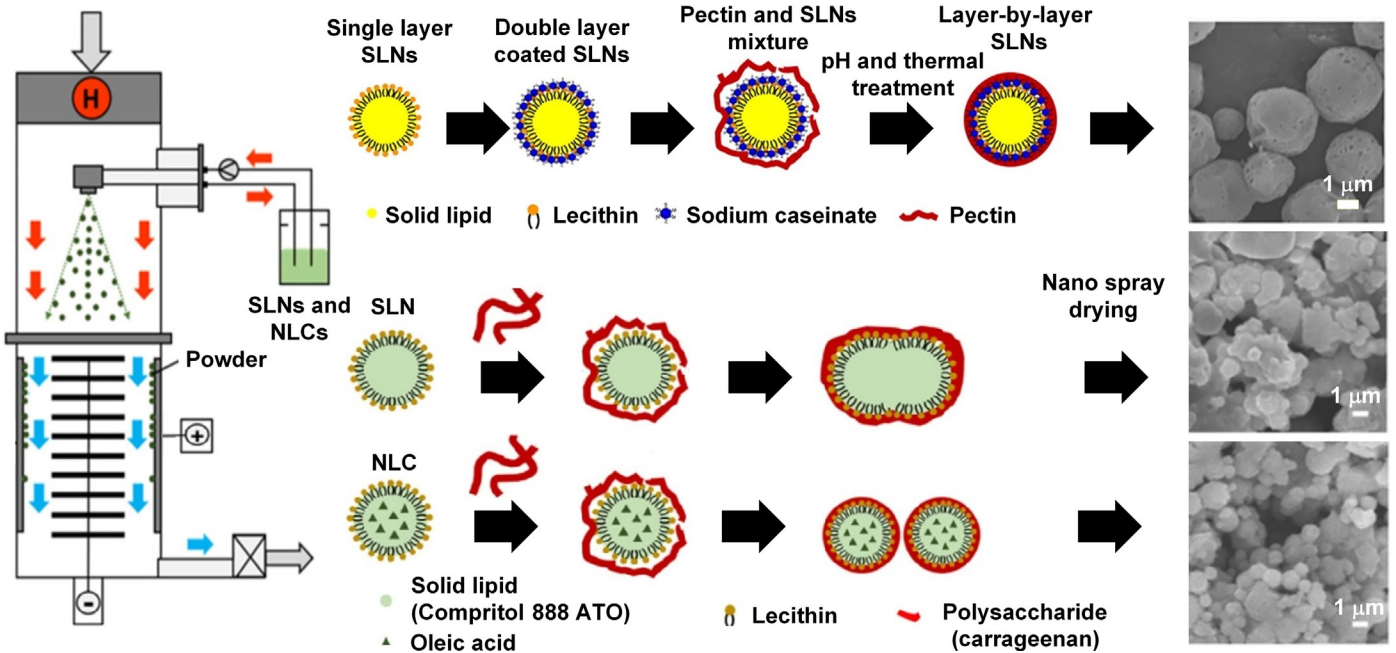

Fig. 19 Schematic diagrams of the fabrication of layer-by-layer coated solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) with nano spray drying. *(Based on Wang, T., Hu, Q., Zhou, M., Xia, Y., Nieh, M.-P., Luo, Y. (2016). Development of "all natural" layer-by-layer redispersible solid lipid nanoparticles by nano spray drying technology.* European Journal of Pharmaceutics and Biopharmaceutics, 107, *273–285; Wang, T., Hu, Q., Zhou, M., Xue, J., Luo, Y. (2016). Preparation of ultra-fine powders from polysaccharide-coated solid lipid nanoparticles and nanostructured lipid carriers by innovative nano spray drying technology.* International Journal of Pharmaceutics, 511, *219–222).*

essential to obtain well-separated uniform and spherical particles after nano spray drying (Wang, Hu, Zhou, Xia, et al., 2016). Chang, Wang, Hu, and Luo (2017) proposed zein-caseinate-pectin complex nanoparticles as potential oral delivery vehicles for curcumin, owing to their high encapsulation efficiency, slow release, enhanced antioxidant activity, and exceptional redispersibility after drying. The chemically cross-linked protein–polysaccharide nanoparticles revealed an excellent GI stability.

Xue et al. (2017) fabricated organic solvent-free SLNs by emulsifying melted stearic acid as solid lipid matrix via sonication directly in an aqueous phase containing NaCas and pectin, followed by pH adjustment and thermal treatment to reinforce the polymeric coating network. The nano spray-dried powders exhibited spherical morphology, smooth surface, and narrow size distribution in a range of 500 to 800 nm. The colloidal SLNs could be effectively redispersed in water after nano spray drying without variation of dimension, shape, and morphology. In a follow-up study, Xue et al. (2018) encapsulated curcumin in biopolymer-emulsified SLNs and produced nano spray-dried powders of 0.5 to 1 μm size with uniform distribution and no visible aggregation. To sum up, it can be said that the bioactive-loaded SLNs can be successfully processed into stable powders by nano spray drying, which holds a promising potential for future applications of lipophilic nutrients.

3.6 Salts

Mineral nutrients and salts are essential constituents for human health as they play an important role in the development of bones and teeth and strengthen human muscles. For example, sodium (Na) regulates osmotic pressure, nerve function, acid-base balance, and blood pressure (Oprea & Grumezescu, 2017). Table 14 lists some application examples of nano spray dried salt substances that have a potential use in food applications.

Li et al. (2010) demonstrated the basic ability to nanostructure salt substances by nano spray drying using the example of sodium chloride (NaCl) solutions. Particle sizes from 517 to 993 nm were produced at salt concentrations of 0.1% to 1% (w/w) using a 4.0-μm spray mesh (Fig. 20A). Moncada et al. (2015) used higher concentrations, that is, 3%, 5%, 10%, and 20%, to achieve a higher salt yield. Approximately 80% of the NaCl particles were between 500 and 1900 nm, when drying a 3% (w/v) solution. Fig. 20B and C illustrates the morphology of the fine salt particles. In particular, Moncada et al. (2015) investigated the effect of sensory and

Table 14 Process conditions for nano spray drying of salt solutions (– = not available).

Substance	Food application	Solid concentration (w/v)	*T* in/*T* out (°C)	Drying gas (L/min)	Particle size (μm)	Reference
Sodium chloride (NaCl)	Surface-salted cheese crackers	3%	95/-	125	0.5–1.9	Moncada et al. (2015)
Sodium chloride (NaCl)	Model of water-soluble salt	0.1%–1.0%	100/-	100	0.5–1.0	Li et al. (2010)
Disodium phosphate (Na_2HPO_4)	Anticaking agent, pH adjustment	0.1%	120/-	120	0.5	Schmid et al. (2011)
Tartaric acid ($C_4H_6O_6$)	Acidifier	10%	80/34–46	133	1–4	Büchi Labortechnik AG (2009)
Sodium sulfite (Na_2SO_3)	Food preservative	1%	80–110/ 43–51	133	0.5–2	Büchi Labortechnik AG (2009)

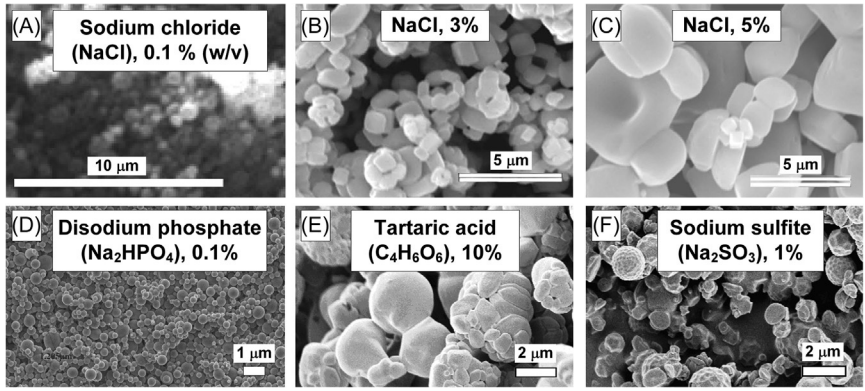

Fig. 20 SEM pictures of nano spray-dried salt particles obtained with the Nano Spray Dryer B-90. (A) Sodium chloride (NaCl), 0.1% (w/v) aqueous solution (Li et al., 2010); (B) NaCl salt, 3% (Moncada et al., 2015); (C) NaCl salt, 5% (Moncada et al., 2015); (D) disodium phosphate (Na_2HPO_4), 0.1% (Schmid et al., 2011); (E) tartaric acid ($C_4H_6O_6$), 10% (Büchi Labortechnik AG, 2009); (F) sodium sulfite (Na_2SO_3), 1% (Büchi Labortechnik AG, 2009).

microbiological characteristics of surface-salted cheese crackers. Nano spray-dried salts resulted in a significantly higher level of preferred saltiness than the control. Interestingly, the small particles produced by nano spray drying would reduce sodium intake by 25% to 50% if used in surface-salted cheese biscuits. By reducing the particle size, the dissolution rate and the solubility will increase.

Schmid et al. (2011) examined the possibility of producing submicron particles of disodium phosphate (Na_2HPO_4), which is used mostly in foods to adjust pH. Its presence also prevents coagulation in the preparation of condensed milk. Similarly, it is used as an anticaking additive in powdered products. Fig. 20D shows a SEM photograph of nano spray-dried Na_2HPO_4 with a mean particle size of about 500 nm using a highly diluted solution of 0.1% (w/v).

Büchi Labortechnik AG (2009) provides supplementary application notes for sodium sulfite (Na_2SO_3) or tartaric acid ($C_4H_6O_6$), which demonstrates the versatility of nano spray drying. Sodium sulfite, for example, is used in foods as a preservative and antioxidant to prevent the discoloration of dried fruits. Tartaric acid is found in many fruits, especially grapes. Its salt, potassium bitartrate, develops naturally during wine production. It is most likely recognized by wine drinkers as the "wine diamonds," the small crystals that form spontaneously on the cork or bottom of the wine bottle. In the

food industry, it is used to acidify many kinds of products like drinks, wine gums, and ice cream. As Fig. 20E and F shows, with these substances at 1% solid concentration, particle sizes are in the range of 0.5 to 4 μm.

4 Conclusions and final remarks

The food industry is increasingly turning to encapsulation technologies to add value to certain bioactive ingredients. Spray drying plays an important role as an encapsulation technology and has evolved considerably in recent years. The main objectives of a food scientist are the production of bioactive-loaded powders with a high yield, maximum encapsulation efficiency and loading, extended storage stability, and controlled release under gastrointestinal conditions.

Innovative spray drying technologies are becoming even more important for food engineers. While the focus was on microencapsulation, the potential of nanoencapsulation is increasingly being investigated. A technological innovation was the introduction of the laboratory-scale Nano Spray Dryer B-90 from the Swiss company Büchi Labortechnik AG in 2009, which enables to produce submicron particles of various bioactive food ingredients with a controllable particle size and adjustable release profile. The implemented core technologies are vibration mesh technology for the production of small droplets of a few microns, electrostatic particle separation for highly efficient collection of submicron particles, and laminar drying gas flow to maintain the stability and activity of heat-sensitive bioactive food ingredients.

Depending on the application, an optimized set of process parameters can be found by trial and error or design of experimental studies. The most important process parameters are the inlet and outlet temperatures, the drying gas flow rate, the spray mesh size, and the solid concentration of the used excipients, stabilizers, and surfactants. This gives food engineers and scientists a whole range of formulation playgrounds. Each application demands a defined set of encapsulation materials that meet the requirements of a particular bioactive food ingredient. The main requirements for the encapsulation wall material are food safety, cost-effectiveness, and water solubility.

The number of publications on nano spray drying of bioactive-loaded nanoparticles for food applications has increased rapidly in the last 10 years. More than 150 contributions have been identified, reviewed, and summarized in this chapter. Nevertheless, the current state of research in nano spray drying for the nanocapsulation of bioactive food ingredients is still at an early

stage compared with pharmaceuticals but is constantly evolving. So far, nano spray drying has been successfully applied in the following nanoscale food applications:

- Production of submicron powders from different encapsulating food-grade wall materials. The submicron particle size range is typically reached with diluted solutions of 0.1 to 1% (w/v) solid concentration. Due to the short drying times and the gentle drying conditions, the particles usually have a spherical shape with a smooth or structured surface.
- Encapsulation of water-soluble vitamins (e.g., vitamin B_{12}, B_9), polyphenols (e.g., curcumin, tyrosol, and resveratrol), and extracts (e.g., from guava leaves and saffron) in different wall materials like sodium alginate, gum arabic, whey protein, albumin, pectin, modified starch, chitosan, and maltodextrin.
- Encapsulation of various nanoemulsions (e.g., eugenol oil, peppermint oil, sunflower oil, coffee bean oil, omega-3 fatty acids, and vitamin E acetate) in polymeric wall materials (e.g., gum arabic, lecithin, zein, sodium caseinate, pectin, whey protein, and maltodextrin) and drying to submicron solid particles.
- Drying of nanogels made of egg yolk low-density lipoprotein and polysaccharides with the encapsulation of curcumin.
- Drying of colloidal solid lipid nanoparticles (SLNs) with encapsulated lipophilic bioactive substances (e.g., curcumin) to enhance their stability and bioavailability.
- Nanostructuring of water-soluble salts (e.g., sodium chloride). Tiny salt particles with a size of a few hundred nanometres are formed, which mainly depend on the droplet size (i.e., the size of the spray mesh) and the solid concentration of the feed.

It is foreseeable that the encapsulation of food ingredients by nano spray drying will continue to grow as instruments become more widespread. In particular, this new technology is easy to use and very versatile and allows parameter studies to be carried out on a laboratory scale. Obviously, more applications are to be expected, as nanoscale food applications are an emerging field. The reduction of the spray-dried particle size to the nanoscale offers many new perspectives for the use in functional foods such as carotenoids, polyphenols, minerals, colorants, flavors, antioxidants, and vitamins. Future work will extend the application spectrum, especially with regard to the encapsulation of nanoemulsions containing lipophilic bioactive food ingredients.

In order to further explore the potential of nano spray drying, it is desirable to commercialize this technology on an industrial scale. There is an increasing need to scale up the process to larger powder quantities, for example, by multiplying the number of vibrating mesh nebulizers. Further technological innovations are expected in atomizer technology to further reduce the droplet size.

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