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REVIEW ARTICLE

Nanotechnology Application in Food Science and Nutrition and Its Safety Issues; a Review

Chinaza Godswill Awuchi [1], Hannington Twinomhwezi [1] ,Shivam Choudghal [2] , Mohammad Gayoor khan [3], Umama Yezdani [4] , Mulla Vasim Akram 5
Department of Physical Sciences, Kampala International University, Kampala, Uganda [1]
Department of Pharmacy Practice, ISF College of Pharmacy, Moga Punjab India [2]
Department of Pharmacology, Daksh Institute of Pharmaceutical Science, Chhatarpur,Madhya Pradesh, 471001 –India [3]
Department of Pharmacy Practice, MRM College of Pharmacy, Hyderabad, Telangana, 501510 – India.[4]
Department of Pharmacy Practice, RAO'S College of Pharmacy, Nellore - 534320 Andhra Pradesh India 5
Corresponding Author : Shivam Choudghal

ABSTRACT

Nanotechnology applications have developed with rising needs for use of nanoparticles in food science, nutrition, nutraceuticals, food microbiology, nutrient delivery, among others. Nano-based "active" and "smart" food packaging confers numerous benefits compared with conventional methods of packaging. Nanocarriers including inorganic nanocarriers such as metallic nanostructures like quantum dots, and organic nanocarriers such as polymer nanoparticles and lipid-derived nanoparticles like liposome, nanoemulsions, carbon-based nanocarrier, dendrimers, and hydrogels, have been widely applied in foods. Numerous natural and synthetic polymers used as nanoencapsulating delivery systems are in use and enhanced for better preservation and bioavailability of food active constituents. Conventional methodsuch as solvent emulsification-diffusion, reverse phase evaporation, high-pressure homogenization, and injection methods, and emerging methods such as supercritical fluid, microfluidic channel, self-assembly methods, have been applied. Although nanotechnology applications in foods have raised safety, ethical, and environmental issues, the potentials for its wider application in foods, nutrition, and nutraceuticals are quite promising.

Key words: *Nanotechnology, foods and nutrition, Nanocarriers, nutrient delivery*

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INTRODUCTION

Food science and nutrition have witnessed a boom in state-of-the-art development in recent times. Current development in nanotechnology, including nanoparticles (NPs) and nanomaterials (NMs), have improved many industrial and scientific endeavours including food and pharmaceutical industries, as well as nutrition. Nanotechnology applications have developed with rising needs for use of nanoparticles in food science, nutrition, nutraceuticals, food microbiology; with intense focus on food processing, nutrient delivery, food safety and standardization, foodborne pathogens detection, development of functional foods, extension of shelf-life of foods, and food packaging [1, 2]. Nanoparticles are currently in use in food industries to produce safe and nutritious foods free from contamination, and also to ensure nutrient bioavailability, maintain organoleptic properties, enhance functional properties, and increase consumer acceptance. Nanotechnology is an advanced technology important in enabling development in science, engineering, and technology, including improvement in food application, agriculture, drug delivery, nutrient delivery and bioavailability, and medicine. Nanomaterials can enhance quantitative and qualitative manufacturing of wholesome, safer, healthier, and quality foods which are perishable in nature. Application of nanotechnology in foods is better than the conventional food applications, as it increases the shelf life of foods, improves food quality, improves nutrient availability, and prevents contamination of foods [2, 3]. Nanotechnology applications improve nutrient bioavailability, consistency, texture and taste, attained via enhancement in particle sizes, food nanomaterials surface charge, and likely formation of cluster [1, 2].

Nanotechnology has been applied in the food and nutrition for manipulating nanomaterials and nanostructures for numerous purposes. It plays significant role in agriculture and food, including promoting health using novel nano-techniques, improving food safety and quality, increasing nutrient availability, and contributing to improvement in crops [2, 4]. Due to the exceptional properties (biological, chemical, and physical), large ratio of surface–volume, very low toxicity, and unique solubility in comparison to their micro- and macroparticles, engineered nanoparticles have gained wider applications and attention in foods, sewage treatment, medicine, and nutraceuticals [2, 5, 6]. Nanoparticles of gold (Au), carbon, titanium dioxide ($TiO2$), zinc oxide (ZnO), and silver (Ag) are formulated in tenfolds compared to other nanoparticles because of their antimicrobial properties [6, 7]. In addition, the compelling antibiotic activities of copper oxides (nCuO) nanoparticles have led to their wide applications in nano-biocide production [8]. Nanomaterials have particles between 1 and 100 nm size manufactured using numerous methods, and applied in several fields such as food industries, agriculture, medicine, and electronics [2].

The nanotechnology applications in foods are usually summarized into two major groups; food nano-sensing and food nanostructured ingredients. Nanostructured food ingredients include several areas from raw material processing to packaging of foods [1]. In food processing, the nanostructures/nanoparticles are mostly used as food additives, fillers for enhancing the durability and mechanical strength of packaging materials, antimicrobial agent, carriers for smart nutrient delivery, anti-caking agent, etc., while food nano-sensing is applied to accomplish safety evaluation and better quality of food [1, 9].

NANOTECHNOLOGY APPLICATIONS IN FOOD AND NUTRITION

Nanotechnology application for food packaging

Any desirable material for food packaging should have little or no moisture and gas permeability in combination with biodegradability [1, 10], resistance to mechanical damage, high strength, among other desirable properties. Nano-based "active" and "smart" food packaging confers numerous benefits compared with conventional methods of packaging; from offering improved packaging materials with enhanced mechanical strengths, barrier characteristics, antimicrobial film to nano sensing for detecting pathogens, as well as informing consumers about food safety status [1, 11].

Nanocomposite applications as bioactive materials for packing and coating materials are usually utilized to enhance packing of foods; several scientists have shown interest in evaluating antimicrobe characteristics of organic substances such as bacteriocins, organic acids, and essential oils and their usage in matrix of polymers for anti-microbiological packaging [12, 13]. Nevertheless, most of these organic substances are labile to the rigors of numerous food processing operations that require high temperature and pressure. With the use of nanoparticles of inorganic substances, strong antimicrobial activities are usually accomplished in small concentration and high stability under strict conditions. Recently, it is quite interesting and attractive to use these nanoparticles for food packaging due to their antimicrobial properties [1]. Antimicrobial food packaging is an active packaging that comes in contact with the food or headspace in order to retard/inhibit growth of microorganisms which might be present on the surface of the food [14]. Several nanoparticles of chitosan, copper, and silver, as well as of nanoparticles metal oxide including zinc oxide and titanium oxide have shown antibacterial properties [1, 15].

In addition to nanoparticles application to antimicrobial packaging of foods, nanolaminates and nanocomposite are actively applied for food packaging to confer barrier from mechanical and thermal shock and extend shelf-life of foods. Nanoparticles integration into materials used for packaging foods ensures food quality and extended shelf-life of foods. The objectives of producing polymeric composites include having additional thermostable and mechanical packaging materials. Various organic or inorganic fillers are used to realize enhanced polymeric composites. Nanoparticles incorporation in polymeric compounds ensures the development of more resist and cost effective packaging materials [16, 17]. Using inert nanoparticle fillers including silica (SiO_2) nanoparticles, silicate and clay nanoplatelets, chitosan or chitin into polymeric matrix make the matrix fire resistance, stronger, lighter, and have better thermal characteristics [18]. Antimicrobial nano-sized composite films that are formulated by impregnating the fillers into the polymeric materials provide two-way benefits due to their barrier characteristics and structural integrity.

NANOCARRIERS CLASSIFICATION

Nanocarriers are classified into inorganic-based, organic-based, or combination of organic- and inorganic-based nanocarriers [3, 17]. Inorganic nanocarriers are metallic nanostructures including quantum dots [3]. Organic nanocarriers are polymer nanoparticles and lipid-derived nanoparticles including liposome, nanoemulsions (for example reversed micelle, micelles, etc.), carbon-based nanocarrier (for example, carbon nanotube and fullerenes), and dendrimers. Table 1 summarizes the common nanocarriers used in food science and nutrition (see Table 1).

Table 1: Classification and applications of nanocarriers used in foods and nutrition

Nanocarrier	Class (organic-based or inorganic-based)	Applications and further comments	References
Polymeric Nanoparticles	Organic-based	Polymeric nanocarriers depend on biodegradable and biocompatible polymeric compounds obtained synthetically and naturally. Biodegradable polymeric matrix mostly contain synthetic polymers including polylactic-co-glycolic acids, polyglycolic acid, poly(ε-caprolactone), polylactic acids, poly(amino acid), and polymethyl methacrylate. Biodegradable polymers can also contain natural polymeric materials such as agarose, collagen, sodium alginate, fibrin, and chitosan.	[3, 19 – 21]
Liposomes	Organic-based	Liposomes nanocarriers are concentric lipid-bilayer containing aqueous core bounded with surfactant which can be synthetic or natural phospholipids. Liposome-based nanocarrier systems including archaeosomes, stealth liposomes, virosomes, and immunoliposomes consist of lipid bilayers which are biocompatible and can enhance core materials stability and solubility	[22 – 25]
Dendrimers	Organic-based	Desirable shape and size of a dendrimer depends on branching units' number on recurring units commonly found when various units are used, including poly L-glutamic acid, poly-propyleneimine, polyethylene glycol, polyethyleneimine, chitin, polyamidoamine, and melamine. To improve targeted delivery, core materials are usually conjugated to free surface groups in great number or loaded in interior	[26, 34]
Quantum dot	Inorganic-based	Quantum dot is nanoscale crystal of semiconducting inorganic fluorescent atom having 2 to 10 nm size range. Quantum dots are inert and stable delivery vessel because biomolecules are conjugated to exterior aqueous shells. Cadmium selenide, the semiconducting material, contains a core as well as shell of zinc sulfide (aqueous) which insulates the core, enhancing optical characteristics. Quantum dots are formulated in way that ensures the emission of light from the UV-IF wavelength. The emitted light/wavelengths are too strong and are detected at subcellular levels.	[28, 29]
Nanoemulsions	Organic-based	Nanoemulsions contain 10 to 100 nm droplets sizes and are usually categorized into 2 types depending on the oil/water phases relative spatial orientation. Due to weak particles light scattering in nanoemulsion, it can be suitably incorporated into products that are optically transparent including fortified soft drink and water, sauces, whitening cosmetics, soups	[30 – 32]
Carbon-based nanocarriers	Organic-based	Carbon-based nanocarriers have been in use for quite some time, often in form of carbon nanotubes (CNs). Carbon nanotubes (CNs) are tubular structures derived from carbon and are organized in a graphene sheet shape which is looped in cylinder or covered on the two ends, forming shape of Buckyball. Fullerene, along with tubular types, is popular carbon-based nanocarrier which denote geometric cage-related nanostructures with pentagonal and hexagonal carbon faces	[26, 33, 34]
Hydrogel Nanocarriers	Organic-based	Hydrogels are networks of three-dimensional polymers which absorb great volume of or bio-fluid or water. Water absorption capacity of hydrogels depends on hydrophilic groups presence, including $–SO_3H$, $-CONH_2-$, $-CONH-$, and $-OH$. For food/drug delivery, polymeric materials such as poly-N-isopropylacrylamide, poly(vinyl pyrrolidone), chitosan, poly (vinyl alcohol), alginate, and poly(ethylene oxide) are extensively used for producing crosslinked networks. The networks can be influenced by temperature, pH, light intensity, and electric field.	[35 – 39]

Polymeric Nanoparticles. Nanoparticles of polymers depend on biodegradable and biocompatible polymeric compounds obtained synthetically and naturally. Biodegradable polymeric matrix mostly contain synthetic polymers including polylactic-co-glycolic acids, polyglycolic acid, poly(*ε*-caprolactone), polylactic acids, poly(amino acid), and polymethyl methacrylate [3]. Biodegradable polymers can also contain natural polymeric materials such as agarose, collagen, sodium alginate, fibrin, and chitosan [19]. Additionally, polymeric materials which give controlled release of drug of core polymeric materials are attractive and have also resulted in popularizing nanoparticles of polymers for vaccine delivery and cancer treatment [20]. The biological, chemical, and physical properties of nanoparticles of polymers, together with their flexibility, made them very appropriate for incorporation with bio-materials, including growth factors and genetic material [21].

Liposomes. Liposomes are nanocarriers which are concentric lipid-bilayer containing aqueous core bounded with surfactant which can be synthetic or natural phospholipids. They are categorized according to their structures as unilamellar vesicles (ULVs), oligolamellar vesicles (OLVs), as well as multilamellar vesicles (MLVs). According to ULVs sizes, they can be divided additionally as giant unilamellar vesicles (GUVs) (diameter > 1,000 nanometer), large unilamellar vesicles (LUVs) (diameter >100 nanometer), medium unilamellar vesicles (MUVs), and small unilamellar vesicles (SUVs) (diameter 20–100 nanometer) [22]. Liposome-based nanocarrier systems including archaeosomes, stealth liposomes, virosomes, and immunoliposomes consist of lipid bilayers which are biocompatible and can enhance core materials stability and solubility [23, 24, 25].

Dendrimers. Dendrimers are macromolecular compounds which are monodispersed and are made of an inner core rounded by repetitive branched molecules. They are structured from monomers using divergent or convergent methods of polymerization. Desirable shape and size of a dendrimer depends on branching units' number on recurring units commonly found when various units are used, including poly L-glutamic acid, poly-propyleneimine, polyethylene glycol, polyethyleneimine, chitin, polyamidoamine, and melamine [26]. To improve targeted delivery, core materials are usually conjugated to free surface groups in great number or loaded in interior [27].

Quantum Dot. Quantum dot is nanoscale crystal of semiconducting inorganic fluorescent atom having 2 to 10 nm size range. Cadmium selenide, the semiconducting material, contains a core as well as shell of zinc sulfide (aqueous) which insulates the core, enhancing optical characteristics. Quantum dots are formulated in way that ensures the emission of light from the UV-IF wavelength. The emitted light/wavelengths are too strong and are detected at subcellular levels [28, 29]. Additionally, quantum dots are inert and stable delivery vessel because biomolecules are conjugated to exterior aqueous shells [29].

Nanoemulsions. Nanoemulsions contain 10 to 100 nm droplets sizes and are usually categorized into 2 types depending on the oil/water phases relative spatial orientation. Micelles are droplets of oil suspended in water phase and known as "oil-in-water (O/W) nanoemulsion", while reversed micelles which contain droplets of water suspension in oil phase and are known as "water-in-oil (W/O) nanoemulsion" [30]. Oil-in-water nanoemulsions are often stable kinetically with slight turbidity to transparency. Owing to weak particles light scattering in nanoemulsion, it can be suitably incorporated into products that are optically transparent including fortified soft drink and water, sauces, whitening cosmetics, soups [31, 32].

Carbon-Based Nanocarriers. Carbon-based nanocarriers have been in use for quite some time, often in form of carbon nanotubes (CNs). Carbon nanotubes (CNs) are tubular structures derived from carbon and are organized in a graphene sheet shape which is looped in cylinder or covered on the two ends, forming shape of Buckyball [26]. Two carbon-based configurations include multiwalled nanotubes (MWNTs) and single-walled nanotubes (SWNTs). While MWNT is made of two or more concentric shells of graphene cylindrical sheets round centralized hollow core, single-walled nanotubes are made of single cylindrical graphene [33]. Based on functionalization, the CNs are additionally categorized as surfactant-grafted, solvent-dispersed, ligand-attached, and target-oriented. Fullerene, along with tubular types, is popular carbon-based nanocarrier which denote geometric cage-related nanostructures with pentagonal and hexagonal carbon faces [34].

Hydrogel Nanocarriers. Hydrogels are networks of three-dimensional polymers which absorb great volume of or bio-fluid or water. Water absorption capacity (WAC) of hydrogels depends on hydrophilic groups presence, including $–SO_3H$, $-CONH_2-$, -CONH-, and -OH [35]. The polymer networks' crosslinks are made available by physical entanglements, van der Waals interactions, dipole-dipole interactions, hydrogen bonds, and covalent bonds [36]. The polymer networks' crosslinks can be characterized into chemical tie-points/junctions, and crystallites or physical entanglements [37]. For drug delivery, polymeric materials such as poly-*N*-isopropylacrylamide, poly(vinyl pyrrolidone), chitosan, poly (vinyl alcohol), alginate, and poly(ethylene oxide) are extensively used for producing crosslinked networks. The networks can be influenced by temperature, pH, light intensity, and electric field [38, 39].

Nanotechnology applications in food processing and formulations

Nanostructured recipes and ingredients have been formulated with expectations that the nanosized food ingredients will provide enhanced consistency, texture, and taste. Nanotechnology applications in foods increase shelf-life of foods and reduce food wastage due to contamination by microorganisms [1, 9, 40]. Currently, many nanocarriers are used as delivering agents for delivering food additives in foods without restructuring their basic morphological structures. The size of particles can influence delivering of bioactive compounds to numerous targeted sites in the human body system; report has it that in several cell lines, the submicron-sized nanoparticles alone are effectively absorbed, unlike microparticles which are of larger sizes [1, 9, 40, 41]. Ideal delivering system for foods should exhibit the three properties outlines as follows:

a) ensures availability at specific rate and target time,
b) efficiently maintains active compound at appropriate level for long time (under storage conditions), and
c) ability of precisely delivering active compound at target site

Nanotechnology application in formulation of simple solutions, emulsions, association colloids, encapsulation, and biopolymeric matrices provide efficient deliveries which have all the required qualities as stated. Nanosized polymeric materials are currently showing signs of replacing conventional materials used for food packaging in food industries. Nanosensors are applied in proving occurrence of microorganisms, mycotoxin, and contaminants in foods [41, 42].

Nanoparticles are known to show improved release and encapsulation efficiencies than conventional system of encapsulation. Nanoencapsulation controls active agents release, masks tastes and odors, controls active ingredients interactions with the foods, ensures availability at specific rates and targeted time, and protects them from heat, moisture [9, 40, 42], biological/chemical breakdown while in usage, storage, and processing, as well as similarly show compatible with other substances within food matrix [40, 42, 43]. Additionally, the delivery system has the capability to deeply penetrate tissues because of their minute sizes and therefore provide efficiency in delivering active compounds to specific and target site [44]. Numerous natural and synthetic polymers used as nanoencapsulating delivery systems are in use and enhanced for better preservation and bioavailability of active constituents of foods. Additionally, nanotechnology importance in food processing is assessed through putting its role into consideration in the enhancement of foods in terms of food shelf-life, nutritional values of food, taste of foods, appearance of foods, and texture of foods. Nanotechnology has not only touched all these aspects but has also led to significant improvements in foods conferring novel qualities to the foods.

Table 2: Common nanotechnology used for encapsulating and delivering functional ingredients

Nanotechniques	Notable Examples	Features
Liposome	Cationic lipid integrated liposome modified using acid-labile polymeric HPG (hyper-branched poly(glycidol))	It is used as delivery vehicle for hydrophilic molecules in the aqueous interior, or hydrophobic molecules in a bilayer. [45, 46, 47]
Hydrogel	Hydrogel of protein	Easily added to capsules, can protects components from harsh environmental conditions, and can deliver drugs as a response to environment stimuli including temperature and pH. [48]
Edible coating	Edible coating formulated with gelatin nanoparticles and cellulose nanocrystals. Nanosilica/Chitosan coatings. Chitosan-nano-SiO2 film. Lysozyme/Alginate nanolaminate coatings.	To preserve the quality of fresh foods during extended storage. [1, 49, 50, 51, 52]
Nanoemulsion	Nanoemulsion formulated with β-Carotene. Oil-in-water and Water-in-oil nanoemulsions.	Better stability to separation due to gravity and also to aggregation of droplet; improved oral bioavailability; higher optical clarity. [53, 54]
Inorganic nanoparticles	Mesoporous silica NPs	Shows good encapsulating ability; their rigid surface provides controlled functionality. [46]
Polymer micelle	Polymeric micelles of methoxy poly(ethylene glycol) palmitate. Polymeric micelles of poly (ethylene glycol)-block-poly(caprolactone) [PEO-b-PCL].	Solubilizes water-insoluble substances in hydrophobic interior, low toxicity, high solubility. [55, 56]

Appearance, taste, solubility, and texture of foods

Nanotechnological applications in food system provides many options to enhance the quality of foods, including food taste, texture, and utilization. Food quality are often influenced by the food components such as carbohydrates, proteins, fats, moisture, vitamins and minerals, etc. [57 – 66] and can be improved with nanotechnology. Nanoencapsulation is broadly used to enhance the retention and release of food flavor as well as deliver culinary balancing [1, 47]. In 2014, Zhang and his colleagues made use of nanoencapsulation for anthocyanins (extremely unstable and reactive plant pigment) which have several bio-activities [67]. Nanoencapsulating molecules of cyanidin-3-O-glucoside (C3G) in innermost cavities of seed of apo recombinant soybean H-2 subunit ferritin (rH-2) enhanced photostability and heat stability. Rutin, a dietary flavonoid, has significant pharmaceutical activities, however, it has limited applications in foods because of poor solubility. Nanoencapsulation with ferritin nanocages improved the UV radiation stability, thermal stability, and solubility of rutin trapped in ferritin in comparison with free rutin [1, 2, 68]. Nanoemulsion application in delivering fat-soluble bioactive components is more common as they are made with natural food recipes using common methods of production, and could be formulated to improve bioavailability and water-dispersion [69].

In comparison with large particles that release encapsulated components very slow over a period of time, nanoparticles offer promising way to improve bioavailability of nutraceutical components because of their small subcellular size resulting in better drug bioavailability. Several metallic oxides including silicon dioxide (SiO_2) and titanium dioxide have been used conventionally as flow or color agents in foods [2, 70]. Nanomaterials of silicon dioxide are among most nanomaterials used in foods as nanocarriers of fragrance and flavor in foods [70, 71].

Nutritional value improvement

Most bioactive substances like carbohydrates, lipids, vitamins, and proteins have high sensitivity to extreme acidic environments and enzyme activities of the digestive system, especially duodenum and stomach. Nanoencapsulation of the bioactive compounds enables their resistance against adverse conditions, and allows their readily assimilation in foods and body; these properties are difficult to attain in non-nanoencapsulated form because these bioactive compounds have low solubility in water. Tiny edible capsules formulated at nanoscale aimed at improving delivery of some micronutrients and medicines in regular foods are have been made to provide considerable health benefits [1, 2, 72, 73]. Nano-structuration, nano-emulsification, and nanocomposite are various techniques used for encapsulation of food substances in nano-sizes to deliver nutrients more effectively, including antioxidants and protein for precise targeted nutritive and health improvement. Polymer nanoparticles have been shown as suitable for nanoencapsulation of biological active compounds, such as vitamins and flavonoids, for their protection and transportation to targeted functions and uses [72 – 74].

Preservations and shelf-life extension

In functional foods in which bioactive constituents usually get broken-down and thereafter result in inactivation because of hostile environmental conditions, nanoencapsulating these bioactive constituents extends food shelf-life by delaying the process of degradation or prevent it till the products are delivered to the targeted sites. Additionally, consumable nanocoatings on several foods may offer barrier to gas exchange and moisture and also deliver anti-browning agents, enzymes, antioxidants, flavors, colors, and may extend the foods shelf-life, even after opening the packaging [1, 2, 43]. Nanoencapsulating functional constituents in droplets usually allows delay in process of chemical degradation through bioengineering properties of their surrounding interfacial layer [75]. For instance, the phytochemical curcumin which is the greatest active and lowest stable bioactive constituent of *Curcuma longa* (turmeric) demonstrated decreased antioxidant activities and seen being stable to the rigors of pasteurization (a heat treatment) and at various ionic strengths upon nanoencapsulation [75].

Nanocarriers Preparation and Formulation Methods

Many novel and conventional methods are used for nanocarriers preparation and formulations. Methods based on nanoemulsification are mostly used, however, specific methods have to be established for every nanocarrier [35]. The novel and conventional methods are used for nanocarriers preparation and formulations are explained in this section.

Conventional methods

Solvent Emulsification-Diffusion Method. This method is mostly applied for preparing polymeric-based nanoparticle as well as lipid-based nanoparticle. The oil phases have polymeric substance in organic solvents while aqueous phases have water stabilizer. As they are mixed, molecules of water induce the organic solvent diffusions leading to nanoparticles formation [76]. Solvents used in preparing nanoparticles should be removed. In addition, methods of emulsification used in producing complex nanocarriers require double emulsions [2, 35, 77]. The first step involves adding small aqueous media amount to more voluminous immiscible organic solvents for dissolving the phospholipids. Organic solution with water droplets is then emptied into great volume of the media (aqueous) resulting in a "water-in- oil-in-water (W/O/W) emulsion". A monolayer of lipid assembles round organic droplets leading to aqueous cores bounded in 2 monolayers of lipid separated by organic layers. Unilamellar liposome which has great entrapping of the first aqueous media will then form through removing the organic solvents [78, 79].

Reverse Phase Evaporation. This method was initially demonstrated by [80]; it relies on creating reversed micelles [80]. The reversed micelles exist in aqueous phases having core at the center bounded by lipids, spread in organic solvents. The reversed micelles can be made through dissolving lipids in organic solvents, with addition of small aqueous phase volume, then sonicate the lipid-solvent solution to make inverted micelles (reversed micelles). The organic solvent will then be removed with rotary evaporator leading to viscous gel formation [81]. As soon as sufficient solvent is removed, there is a collapse of the viscous gel, resulting in formation of aqueous vesicles suspension [82]. The demerit of this method (reverse phase evaporation) is that compounds under encapsulation in the vesicles come into contact with organic solvents. As a result, reverse phase evaporation method is not recommended for food ingredients or fragile molecules regardless of the potentials of attaining up to 80% encapsulation efficiency [81].

High-Pressure Homogenization method. This method is commonly applied in preparing lipid-based nanocarriers including solid lipid nanoparticles and nanoemulsions. High shear stress forms high pressure of 100 to 2,000 bar, leading to particles disruption into range of nanometer [83]. The method of high-pressure homogenization is classified into cold homogenization and hot homogenization. The former was made to address the limits in hot homogenizations, caused by high temperature, and has to do the dispersion/solubilization of core materials beyond the nanocarriers of melting point 5 to 10 degree Celsius [76]. The latter provides lesser particle sizes due to the phase reduced viscosity at higher temperatures but can lead to increased rate of degradation of the nanocarrier core materials. Homogenizing at high pressure has high efficiency of encapsulation thus enabling the controlled release of the core material.

Injection Methods. Two methods of injection used in preparing lipid-based nanocarriers make use of ethanol or ether. Mixtures of ether-methanol and diethyl ether are commonly used to dissolve the lipids. The solution of lipid-ether is injected in aqueous media, forming vesicles of nanocarrier [84, 85]. As speed of injection increases, LUVs are formed. One benefit of ether injection method is that it removes solvent from the foods, allowing lengthy time of process-running and making concentrated products of liposomes with high efficiency of entrapment. Nevertheless, the technique generates heterogeneous populations of 70 to 200 nm with necessity for high temperature to nanoencapsulate the organic products [86].

The method of ethanol injection works by dissolving the lipid using ethanol as solvent [87]. The core materials high concentration in aqueous phase are raised by several injections with the lipids' solution. One advantage of ethanol injection is simple and quick MLVs formation [88]. Disadvantages of ethanol injection include high difficulty in removing the ethanol, low concentrations of liposomes, and production of heterogeneous population of 30 to 110 nm [89]. Removing ethanol has considerable difficulty when liposomes are used for bio-cell culturing or treatment of microorganism, as ethanol must be completely removed [89].

Emerging technologies

Supercritical Fluid Method. Supercritical fluid method involves using supercritical fluids for preparation of nanocarriers are used in pharmaceutical studies and industries to address limitations associated with conventional methods [77]. Supercritical fluid could be a gas or liquid, such as CO_2 or water, in conditions more than its thermodynamic critical point of pressure and temperature (for example, CO_2 at 250 bar and 60). Supercritical fluid methods can be categorized into two; anti-solvent precipitation and rapid expansion [76]. Their advantages over conventional methods are enhanced particle morphology design (shape and size) and a decrease in environment impact. Their disadvantage is poor scalability in industrial production, and could result in variable characteristics of particles [90].

Microfluidic Channel Method. This method comprises two silicon wafers like polydimethylsiloxane (PDMS), together attached in vertical arrangement [91]. The microchannel with the width 200 to 1,000 μm, can be carved on a side of the layer of polydimethylsiloxane. Two inlet lines (central inlet and outside inlet) and an outlet can be connected with the microchannel directly. For formulation of liposome, a solution of lipid is directly injected in central inlet whilst the aqueous solutions are directly injected into outside inlet, intersecting with central spot. Liposomes form because of the various shear forces which generate at liquid interface through the varying ratio of flow rate. The process makes use of lipid stream dissolved into solvent transiting between 2 aqueous streams in channel of microfluid. Mixing takes place at interface of the liquid, generating nanocarriers [92]. One advantage of this method is the controlling ease concerning mono-dispersion and vesicle size, though continuous system has not been developed yet.

Self-Assembly Method. Self-assembly Method involves physical process in which already existing disordered molecules or constituents organize themselves in controlled structures through chemical/physical reactions with no external influence [93]. Liposome assembly and protein folding are common self-assembly examples. Self-assembling has been known to have potential of usage in nanotechnological applications, in which desirable structures may be coded into the nanomaterial's properties of interest. However, it is yet to be used in full potentials as experimental conditions where components self-assemble is still insufficiently understood [2, 76, 94].

Nanotechnology in Bioactive Food Ingredients

Bioactive components of foods have likelihood of rapid degradations or inactivation. With nanotechnological formulations, several bioactive components of foods would maintain their benefits from nanoencapsulation procedures that slow the process of degradation and usually prevent it till the components are delivered to the target sites in which their adsorption is required [76, 83]. Several studies have been done on formulating effective delivery system for bioactive compounds, microbial agents, flavors, colors, and also living cells. The delivery systems are tested after ionic strength modification, pH adjustment, heating, or mechanical stress application to evaluate their stability in the conditions they could face in foods [94]. The interactive nature of the matrix of the particle and the nanoencapsulated molecules is the determinant of the release behavior, retention capacity, and stability of the nanoencapsulated molecules. Nanoparticles could be bound chemically to or trapped physically in the matrix of the particle. Amongst the various delivery systems, nanomaterials fabrication will unquestionably solve several difficulties faced by bioactive food ingredients (BFI). Nanomaterials are carefully, intentionally, and meticulously formulated to have specific composition or unique properties at the nano levels, in other words, typical size range of 1 to 100 nm, and either nanostructured with surface/internal nanoscale structure, or nano-object confined in 1 to 3 nanoscale dimensions. Nanotechnology applications and advancement have effects on key aspects of foods including synthesis of novel foods at molecular level, cell-based foods, ingredients, and food safety. The nanotechnology mostly used for bioactive food ingredients delivery includes nanostructured lipid carrier (NLC), liposomes, SLNs, nanotube, micelles, nanoparticles, etc. [94 – 96].

Potential nanotechnology advantages for BFI delivery:

a) Developing novel materials for food packaging, such as nanocomposite polymer film, which allow the prevention of contamination, enhance thermal stability, offer stronger mechanical properties, and give better transmission barrier against water vapor and oxygen [94, 95].
b) Zoonotic diseases detection.
c) Product traceability.
d) Enhanced BFI and micronutrients delivery [94, 97].
e) Food safety intervention.
f) Controlled release of bioactive food ingredients, such as omega-3 fatty acids, etc. [94].
g) Encapsulating food bioactive compounds [98].
h) Improved bioavailability and absorption of BFI and other bioactive compounds in foods [99].

Safety Issues Associated with Nanotechnology Applications in Foods and Nutrition

Despite nanotechnological advantages in food industries, safety concerns regarding nanomaterials in foods are not overlooked. Rapid growth of nanotechnology applications in foods have raised safety, policy, regulatory, ethical, and environmental issues. Several studies have been done on safety issues associated with nanomaterials in foods with more emphasis on likelihood migration of nanoparticles from food package to foods, as well as their impacts on the health of consumers [100]. Though food materials are usually held as generally regarded as safe (GRAS), more studies should be done to evaluate the risks of their nanoscale as nanoparticles properties are different from those of macroparticles. Additionally, the minute sizes of nanoparticles could increase bioaccumulation risks in body tissues and organs [101]. Free nanocarriers usually pass through cellular and intestinal barriers, and may result in increased bioaccumulation of foreign matters in human tissues, blood, and cells. Nanoparticles of silica that are commonly used for anti-caking may be cytotoxic to cells of human lungs when exposed [1, 2, 94, 100]. Lots of factors influence dissolution including aggregation, surface energy, concentration, and nanoparticles surface morphology. Current nanotechnological developments have encouraged many nano-based industrial and scientific formulations, as markets for products made with nanomaterials keep recording consistent growth and incessant attraction [1]. Nanomaterials might present significantly different biological, chemical, and physicochemical properties in comparison with their conventional food materials; some these properties are either unknown or not fully understood and as a result could pose unpredictable hazard.

Likely risks of human direct contacts with nanoparticles via oral route remain considerable concern. Nanocarriers fate in food systems greatly varies based on hydrolysis susceptibility to enzymes involved in digestions and other conditions which may interfere. Increased use of emulsifiers and organic solvents for preparing nanocarriers may pose risks because of their potential toxicities [30, 100]. These organic solvents have to be carefully removed through safe process such as evaporation process; however, traces of the solvents may remain in the foods, posing safety concerns as their actual concentrations are not often known, and may even be below detection limits. Emulsifiers and solvents are considered toxic and not GRAS, although safe levels have been outlined by organizations such WHO, FDA, and EFSA [30]. They still pose risks in certain conditions and levels.

CONCLUSION AND FUTURE PERSPECTIVE

Food science and nutrition have witnessed a boom in state-of-the-art development in recent times. Current development in nanotechnology, including nanoparticles (NPs) and nanomaterials (NMs), have improved many industrial and scientific endeavours including food and pharmaceutical industries, as well as nutrition. Nanotechnology is an advanced technology important in enabling development in science, engineering, and technology, including improvement in food application, agriculture, drug delivery, nutrient delivery and bioavailability, and medicine. Nano-based "active" and "smart" food packaging confers numerous benefits compared with conventional methods of packaging; from offering improved packaging materials with enhanced mechanical strengths, barrier characteristics, antimicrobial film to nano sensing for detecting pathogens, as well as informing consumers about food safety status. Nanocarriers including inorganic-based, organic-based, or combination of organic- and inorganic-based nanocarriers, have been widely applied in food system. Nanostructured recipes and ingredients have been formulated with expectations that the nanosized food ingredients will provide enhanced consistency, texture, and taste. Nanoparticles are known to show improved release and encapsulation efficiencies than conventional system of encapsulation. Numerous natural and synthetic polymers used as nanoencapsulating delivery systems are in use and enhanced for better preservation and bioavailability of active constituents of foods. Many novel and conventional methods are used for nanocarriers preparation and formulations. With nanotechnological formulations, several bioactive components of foods would maintain their benefits from nanoencapsulation procedures that slow the process of degradation and usually prevent it till the components are delivered to the target sites in which their adsorption is required. Although the rapid growth of nanotechnology applications in foods have raised safety, policy, regulatory, ethical, and environmental issues, the advantages and benefits are promising. There are numerous potentials for more applications of nanotechnology in foods and nutrition.

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COMPETING INTEREST

The authors declare no competing interest whatsoever

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