

Nanoparticles in Food Packaging: Opportunities and Challenges



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Abstract Packaging is the last stage of food processing and a successful package is one that protects a product or contents from environment for a period of time with a reasonable cost. The package affects the quality of foods by controlling the degree of factors connected with processing, storage and handling that can act on components of food.

Use of nanotechnology in science brings great opportunities to many industries including food packaging industry. Recently, various engineered nanomaterials such as nanoclays and metallic nanoparticles have been introduced to food packaging as functional additives. Their positive effects on developed packaging materials have been extensively reported.

Nanoclays and metallic nanoparticles are also promising in active packaging technology, an innovative technology for food preservation based principally on mass transfer interactions between systems “food/packaging”. These nanoparticles have been applied to packaging system using different ways. This chapter aims to give an overview about the use of nanoparticles for food packaging and introduce the nanoclay and metallic nanoparticle types. Recent developments on active packaging produced by the use of nanoparticles are summarized. Migration studies and their safety issues are also discussed.

Keywords Metallic nanoparticles · Nanoclay · Migration · Silver · Zinc oxide · Safety

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Introduction

Packaging is the last stage of food processing and a successful package is one that protects a product or contents from an environment for a period of time with a reasonable cost. The package controls the degree of factors relevant with processing, storage and handling which can act on components of food. Conventional food packaging has four major functions which are containment; protection/preservation; communication and utility. The term “containment” means to contain products to enable them to be moved or stored. Products should be contained for delivery from their production place to market or store. Products which are likely to be lost some existing components or contaminated by the environment can be transported with proper packaging.

Fresh or processed foods is exposed to physical damage (shock, vibration, compressive forces, etc.) and environmental damage (caused by exposure to water, gases, light, odors, microorganisms etc.) during storage and transportation. An appropriate packaging ensures protection and reduces these types of damage to the packaged foods. The protection function is crucially important for shelf stable foods in a can or pouch, in order to be stable, especially against microorganisms during the time that the package provides protection. The communication functions of food packaging mainly provided with label. According to country regulation that produced food, the label should contain some information such as the net quantity of the contents, name and address of the manufacturer, nutritional information, distributor, and notice for allergens. So the package identifies the product, also with a special design (shape, color, recognized symbols) behaves like a silent salesman.

Sometimes utility function of packaging is termed “convenience”. The packaging industry should respond to consumer demands change with their life styles. The popularity of food products that offer simplification and convenience have grown in population. For example, microwaveable entrees, oven-safe meat pouches, steam-in-pouch vegetables and pump-action condiment have been introduced and the packages that provide product visibility, resealable and easy disposal have got the importance. Glass, paper, metal, paperboard and polymers (plastics) are the main materials used by food packaging industry. These materials can be used alone or in a combination (composite material or multilayer packaging material). Due to its functional properties (heat sealable, flexibility, transparency etc.), low weight and costs, plastic is the most used material in packaging of foods (Shin and Selke 2014).

As mentioned above, the main functions of the packaging are accepted as to protect the food from contamination and spoilage and enable to transport it. Therefore, the basic expectations from food packaging are that it should be inert (not to release substances into food); don't change the taste, odor, and composition of the food. While, technological developments including nanotechnology contribute to new functions to the food packaging. Active and intelligent packaging methods introduced in food industry. Active packaging method may be defined as incorporation of certain additives into package to maintain or extending product quality and shelf-life, whereas intelligent/smart packaging method is defined as

those packaging systems with the aim of monitoring the condition of packaged foods to give information about the quality of the packaged food. With the help of these new methods, the package can inform the consumer about the condition of the food and may even interact with the food by releasing or absorbing substances. So, food contact material legislation have been revised in many countries and apart from inert packaging, intelligent food contact and active food contact materials have been introduced (Prasad and Kochhar 2014).

Advancement in use of nanotechnology brings great opportunities for many industries including food packaging industry. Recently, various nanoparticles (such as nanoclay and metallic nanoparticles) have been introduced to food packaging as functional additives. Their positive effects on developed packaging materials have been extensively reported. According to the studies, these nanoparticles improved certain properties of packaging material and introduce new functionalities to active packaging method.

In particular, metallic nanoparticles such as silver, zinc oxide, silicon dioxide and titanium dioxide have been extensively studied; silver and zinc oxide with antimicrobial functions have already been commercialized in some applications (Duncan 2011; Ayhan et al. 2015). These nanoparticles are known to be efficient antimicrobial agents because of their unique properties such as high-temperature, stability and low volatility. However, there is a concern with regard to usage in food packaging materials, whether the nanoparticles transfer from the packaging and cause negative health effects. Present chapter aims to give an overview of the use of nanoparticles for polymer based food packaging, introduce the nanoclay and types of metallic nanoparticles and their application methods. Recent developments on active packaging produced by the use of inorganic nanoparticles are summarized, and migration studies on nanocomposite packaging films and their safety issues are also discussed.

Nanotechnology Usage in Food Packaging

Packaging plays a crucial role in maintaining food quality and reducing product waste. There is an increase in the amount of packaging used, but still poor packaging of food has a significant impact on food loss or wasted food amounts. The use of nanotechnology in food packaging is considered to be highly promising, because it has contributed the development of materials with new properties. The combination of nanoparticles with food packaging materials is known to improve packaging performances, such as ultraviolet, oxygen, carbon dioxide, moisture, and volatile barrier attributes and mechanical properties like tensile strength, elongation, young modulus, yield strength, thereby extending the shelf-life of foods. Even use of the nanoparticles in low fractions into traditional packaging materials can improve the initial properties of material (Cushen et al. 2014b; Ayhan et al. 2015). However, these improvements may change depending on some parameters such as the polymer type, the amount, type and properties (shape, size, production method) of

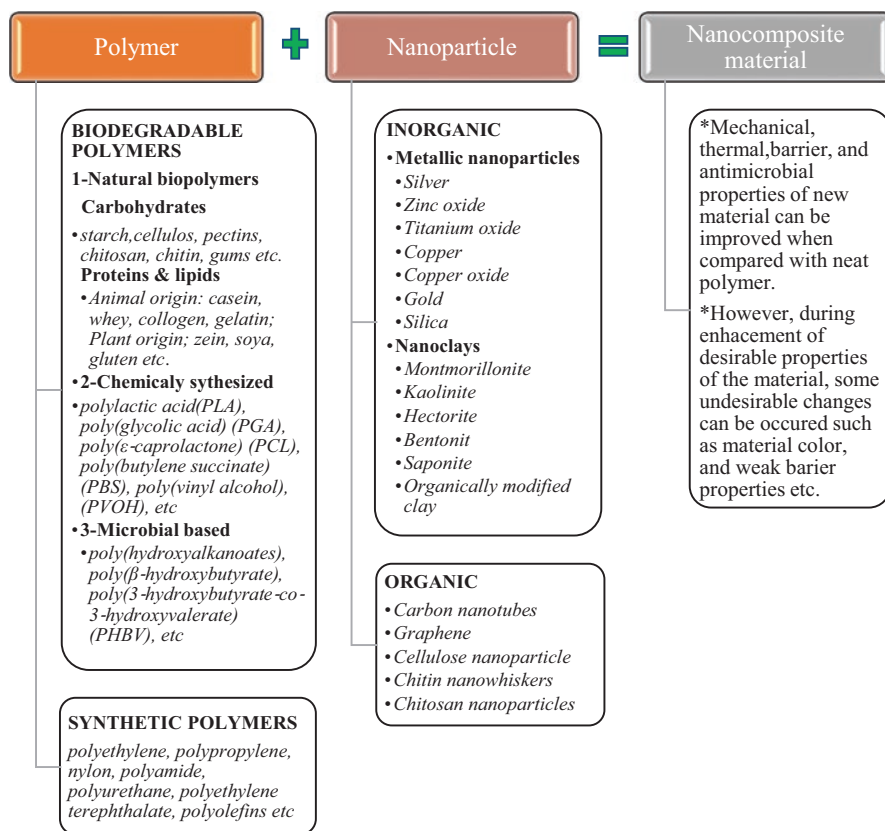


Fig. 1 Classification of polymers and nanoparticles used to produce nanocomposite material

nanoparticle, the method used for the production of the material and the process conditions. Various polymers and nanoparticles can be used for nanocomposite packaging material (Fig. 1).

Figure 1 shows the classification of polymer and nanoparticles which are used for the production of nanocomposite materials. Due to its functional properties such as light weight, cost and heat sealable, plastics (synthetic polymers) are the most used material for food packaging. But extensive usage of the plastics give rise to billion tons of plastic waste is being generated into the environment annually. Generally, decomposition of the plastic based packaging materials is not possible and recycling of them is very difficult. The environmental pollution caused by these products has led to an increasing interest in developing biodegradable packaging materials produced from renewable resources. Efforts are being made worldwide to develop renewable and biodegradable substitutes for non-biodegradable (synthetic polymer based) food packaging materials. Biodegradable polymers, such as polylactide and polycaprolactone, represent an alternative to the conventional synthetic

polymers. However, their cost and the performance of package produced from them restrict their extensive usage.

Nanotechnology is also used in the production of new food packaging materials. The European Union defines ‘nanomaterials as “a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range of 1–100 nm. This definition is a reference for determining and legally clarifying whether a material should be considered as a ‘nanomaterial in the European Union (Rijk and Veraart 2010; Störmer et al. 2017).

Mostly inorganic nanoparticles are used in the production of new food packaging materials in food industry. The purposes of inorganic nanoparticle addition to polymer based food package are given below:

- Improvement of barrier properties via the incorporation of nanoclays.
- Active food packaging applications to increase shelf-life of food, active substances such as metallic nanoparticles (especially nanosilver, zinc oxide and copper) are used
- Enhancement of physical characteristics to make the packaging more durable to environmental conditions (UV blockage, thermally stable material).

The positive effect of addition of nanoparticles to polymers (biodegradable or non-biodegradable) has been extensively reported. Researchers have emphasized that addition of metallic nanoparticles to polymer contribute the material’ antimicrobial and UV barrier properties; and addition of nanoclays improved the material barrier properties against O₂, CO₂, and water vapor permeability. However, when the nanoparticles added to polymer, it is possible that some properties of the material may be weakened, while developing certain features of it. For instance, the addition of ZnO nanoparticles can weaken the mechanical properties of the polymer, while improving the UV barrier properties of polymer. Addition of silver nanoparticles can reduce the light permeability of the material, whereas increase the antibacterial properties of the material at the same time. As mentioned earlier, the enhancement of material properties depends on the amount, type and properties of the added nanoparticle (such as shape, size, production method, surface area) and process conditions used for production of the material.

Production of Nanoparticles

The synthesis methods of nanoparticles is very important as their properties are affected greatly with size and shape. There are two main approach to synthesize nano-size structures: top-down and bottom-up. Nanoparticles are produced with these two approaches. The first one is dividing large compounds to obtain smaller portions (top-down approach), while the other one is condensing of matter in gaseous phase/solution (bottom-up approach). In the first approach, mostly in physical

Physical	Chemical	Biological
<ul style="list-style-type: none"> • Evaporation • Ultrasonication • Irradiation • Laser ablation • Microwave • Thermal decomposition • Electrochemical • Radiolysis 	<ul style="list-style-type: none"> • Chemical reduction • Sol-gel method • Hydrothermal • Inert condensation • Inverse micelles • Colloids • Coprecipitation 	<ul style="list-style-type: none"> • Bacteria (<i>Lactobacillus</i> sp., <i>Cyanobacteria</i>) • Fungi (<i>S. oneidensis</i> MR-1, <i>S. cerevisiae</i>, <i>A. flavus</i>, <i>F. oxysporum</i>) • Algae • Plants • Amino acid • Peptides

Fig. 2 Synthesis methods of nanoparticles

synthesis, materials are breakdown for obtaining matters at submicron size, while atom or molecules are combined with molecular structures in the bottom-up approach, mostly in chemical or biological synthesis. The earlier method to synthesize nanoparticles mostly applied in metallic ones, especially gold nanoparticles which are one of the most studied nanomaterials in many different fields from electronics to foods (Kalpana and Rajeswari 2017; Carrillo-Inungaray et al. 2018).

Nanoparticles can be produced with physical, chemical or biological methods which are used recently in nanotechnology (Fig. 2).

There are different kinds of chemical synthesis reported in the literature such as colloidal method, photochemical, electrochemical and radiochemical reduction, sol-gel method, solvothermal, hydrothermal and sonochemistry synthesis. In chemical methods, reduction of a dissolved metal salt is ensured with the aid of a reducing agent (sodium borohydride, sodium citrate, citric acid, ascorbic acid, carbohydrates, hydrazine, hydroxylamine compounds) in the presence of a stabilizer or capping agent.

Physical methods containing evaporation and condensation can be used for producing some metallic nanoparticles but the energy consumption is higher. Also, laser ablation of metal plates in a solution, and the laser irradiation of colloidal solution can be used to obtain contaminant-free NPs.

In the biologic methods which are more environment friendly than other methods, plant extracts are used to obtain NPs surrounded by proteins or other biomolecules. Microorganisms can be used to produce NPs in different shapes (cubic, spherical, octahedral, tetragonal, wormhole and irregular) by intracellular or extracellular routes. Additionally, microbial enzymes with antioxidant or reducing properties can be used for reduction of metal compounds.

Some molecules have also been utilized for metallic nanoparticle (Ag, Au, Pt and Cu) production with different methods like the peptide mediated reduction of silver ions, the photo reduction of DNA-metal ion complex and the simple seeded mediated growth method (Huang et al. 2007; Kalpana and Rajeswari 2017). While biologic methods are better to control the size of nanoparticles, chemical methods should be preferred for large-scale productions of nanoparticles (Kalpana and Rajeswari 2017; Tamayo et al. 2019). The size is one of the key parameter of the nanoparticles, because it has a crucial role on properties of nanocomposite material. Depending on their size, antibacterial properties, UV barrier properties of material can change.

Inorganic Nanoparticles

Nanoclays

Clay materials are in silicates group (phyllosilicates) and organized into several classes such as kaolinite, smectite, vermiculite, chlorite and micas, as it can be seen at Table 1.

Table 1 Classification of silicates (Khalid et al. 2016)

Silicates
1. Tectosilicates (zeolites, quartz, feldspars)
2. Phyllosilicates (sheet silicates)
(a) 1:1 Phyllosilicates (kaolinite, serpentine)
(b) 2:1 Phyllosilicates
• Talc-pyrophyllite,
• Smectites
– Dioctahedral smectites (montmorillonite, beidellite, nontronite)
– Trioctahedral smectites (saponite, hectorite, saunonite)
• Vermiculites
• Chlorites
• Micas
(c) 2:1 inverted ribbons (sepiolite, polygorskite)
3. Other silicates

Clays consist of silicon, aluminum or magnesium, oxygen and hydroxyl with various cations. These ions and OH groups are organized into two dimensional structures as layers. Thus clay minerals are also called layered silicates or phyllosilicates because of their structural framework. The silica and alumina layers are 1 nm thick and joined together in various proportions and stacked on top of each other in certain way with a variable interlayer distance. The clay minerals can be classified into three different types based on the condensation ratio of silica to alumina sheet as 1:1, 1:2 and 2:2 types (Ke and Stroeve 2005; Azeez et al. 2013).

Nanoclays are nanoparticles of sheet mineral silicates with layered structural units that can compose complicated clay crystallites by stacking these layers (Lee and Diwakar 2012). Montmorillonite (MMT) and halloysite (HNT) are nanoclays with platelet and tubular structure respectively. Both clays have been extensively investigated in food packaging applications as fillers and carriers of active compounds (Tornuk et al. 2018). The MMT belongs to the structural family known as the 2:1 phyllosilicates, and HNT is 1:1 phyllosilicates.

The chemical composition of MMT is approximately $\text{Na}_{1/3}(\text{Al}_{5/3}\text{Mg}_{1/3})\text{Si}_4\text{O}_{10}(\text{OH})_2$ (Pinnavaia and Beall 2000), however it can be varied depending on geographic location and deposit strata. Montmorillonite owes special attention among the smectite group due to its ability to exhibit extensive inter layer expansion or swelling, because of its special structure as shown in Fig. 3.

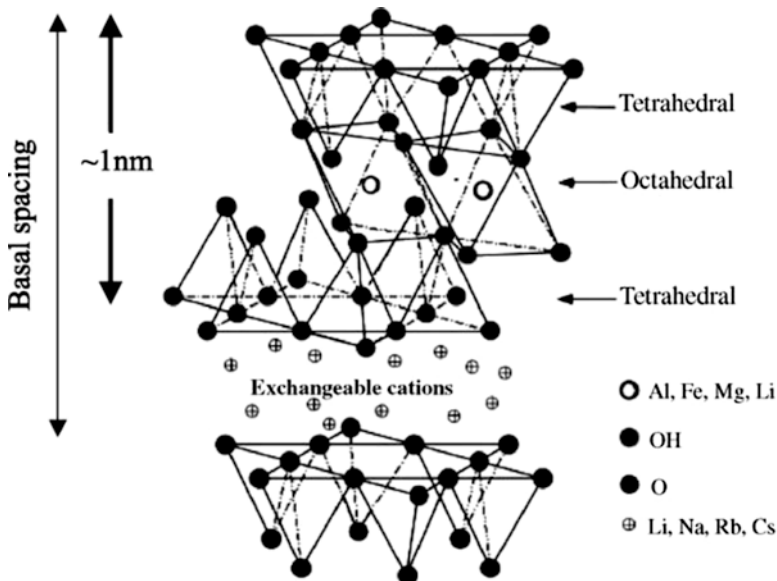


Fig. 3 Basic structure of a 2:1 phyllosilicate (adapted from Ray and Okamoto 2003)

The crystal structure of montmorillonite consists of a single aluminum hydroxide octahedral sheet is located between two layers of silicon oxide tetrahedral sheets (Yalcin and Cakmak 2004). So that the apical oxygen atoms of the tetrahedral sheets are all shared with the octahedral sheet. An overall negative charge is provided by isomorphous substitution of aluminum for silicon in the tetrahedral sheet and iron/magnesium for aluminum in the octahedral sheet. As the surface between the layers is negatively charged it attracts cations such as Ca^{2+} , Fe^{2+} and Na^+ . They form layer positively charged between the negatively charged areas. The silicate layers of MMT are planar, solid about 1 nm in thickness with high aspect ratio and large active surface area (700–800 m^2/g) (Azeez et al. 2013). The enormous surface area available for interaction between polymer and clay allows polymer chains to transfer stress into filler particles. Additionally, high aspect ratio particles may help to recuperate the barrier properties of membranes by increasing the tortuosity of the material.

Metallic Nanoparticles

Metallic nanoparticle usage has recently gained increasing interests due to antimicrobial activities of the nanoparticles. Properties of metallic nanoparticles depend on source of metal (Ag, Zn, Cu, TiO_2), synthesis method, size (0–100 nm) and shape (spherical, rods, wires etc.). The possible antimicrobial action mechanism of the metallic nanoparticles has already been discussed (Fernández et al. 2010; Espitia et al. 2012). These are:

1. release of antimicrobial ions from nanoparticles and interaction of nanoparticles with microorganisms
2. damaging the integrity of bacterial cell
3. formation of reactive oxygen species (ROS) by the light radiation (Fernández et al. 2010; Espitia et al. 2012).

Especially for TiO_2 nanoparticles, UV activation is needed for antimicrobial effect (Zhang et al. 2014). Metallic nanoparticles have been applied different ways on food by researchers (Fig. 4).

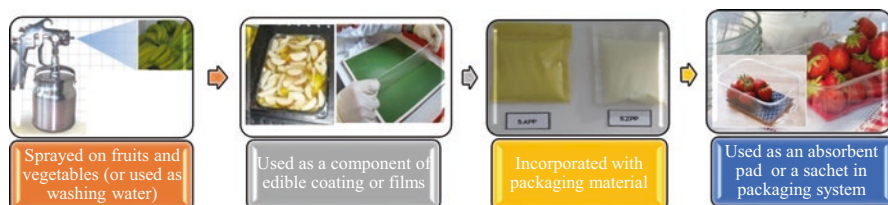


Fig. 4 Application of metallic nanoparticles

Ouzounidou and Fragiskos (2011) sprayed nano Cu on parsley leaves and reported that Cu solution increased shelf life of parsley. Hedayati and Niakousari (2015) prepared gum arabic/silver nanoparticle coating solution and applied on green bell peppers. The coating significantly hindered growth of microorganisms and physicochemical losses, and also enhanced the shelf life of the peppers. Hu et al. (2011) produced PE based nanocomposite film and packaged ethylene-treated mature kiwifruit. Fernández et al. (2010) used cellulose/nano silver absorbent pads and located in trays of fresh-cut melon and reported that absorbent pad application shows lower microbial load. Packaging application using metallic nanoparticles has a great importance in food industry, especially because of their inhibiting effect on some microorganisms. The antimicrobial mechanisms of metallic nanoparticles in dense polymers or thermoplastics used in food packaging materials mainly based on the releasing of ions.

The metallic nanoparticles are also used in intelligent/smart packaging which contains chemical or bio-sensors to be able to monitor the changes in quality or safety of foods. Leakage, level of some particular gases like carbon dioxide, pH, storage time and temperature can be determined by smart packaging systems and biosensors. Fu et al. (2008) investigated a biosensor based on an Au/silicon nanosize-rod for the detection of *Salmonella*.

Production Methods of Nanocomposite Packaging Materials

The nanocomposite food packaging materials are produced according to different methods combining inorganic particles with polymers. The efficiency of these methods is related to inorganic nanoparticle addition processes. These processes are involved in melt blending, in situ-polymerization or solution blending as techniques to incorporate the nanoparticles. According to the form and the final destination of the package, other techniques are introduced in the transformation process such as extrusion-blow molding, compression molding, injection molding or evaporation (Fig. 5).

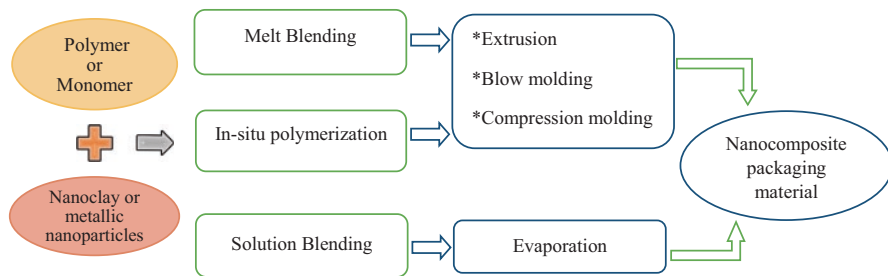


Fig. 5 Nanocomposite packaging material production with different production methods

The production method of nanocomposites has an important role in how the inorganic nanoparticles are distributed through the polymer matrix. The possible distribution of the clay nanoparticles and its possible effect on barrier properties of the resulting materials has been reported (Alexandre and Dubois 2000). An important task in the preparation of nanocomposite material is to achieve uniform dispersion of nanoparticles in the polymer matrix (Guo et al. 2018). When the higher amount of nanoparticle is used, the agglomeration of nanoparticles may be occurred. Generally, this requires chemically modifying the nanoparticle surface so that more homogeneous dispersion occur within polymer. Each of the production method has its own advantages and disadvantages.

Solution Casting

Solution casting is a solvent based process in which the polymer are soluble inside a proper solvent and then nanoparticle mixed with this solution and homogenization is applied for a time. Then solution is poured in a flat mold and solvent is evaporated. This technique is mostly favorable for lab scale production of nanocomposite films. The major advantage of this method is that it offers the possibility to synthesize intercalated nanocomposites based on polymers with low or even without polarity (Azeez et al. 2013). The drawbacks of this technique is that the intercalation process only occurs for certain polymer/nanoparticle/solvent combinations and plentiful amounts of organic solvents are typically required, which may be environmentally unfriendly and costly production (Guo et al. 2018).

Melt Blending

The melt blending technique involves the melting of polymer granules to form a viscous liquid and then the nanoparticles are dispersed into the polymer matrix by high shear rate combined with diffusion at high temperature (Chen 2011). Generally, extruders (it might be single or twin screw) are used for compounding to achieve a uniform dispersion of nanoparticles in polymer matrix. Then, produced nanocomposite granules are diluted with neat polymer to get desired nanoparticle ratio in polymer matrix, and a second process is applied (such as extrusion blow molding, injection molding or compressing molding) to create packaging material (Fig. 2). This technique is considered industrially feasible, because existing equipment which are used for producing food packaging material can be adaptable to nanocomposite material production, and compatible with current industrial processes such as extrusion and injection molding, especially for synthetic polymer based materials fabrication. When compared with solution casting method, the absence of solvents reduces the environmental concerns and provides better mixing of polymer and nanoparticle fillers. There are some important parameters for the production of

the nanocomposites with the melt blending technique. These are extruder processing conditions such as type of extruder, rate of feed, temperature profile, screw speed, die pressure, mixing time and the presence of oxidative environment, material grades and contents, as well as the chemical nature of the nanoparticles and polymers (Guo et al. 2018).

In Situ Polymerization

In situ polymerization is a widely-applied synthesis technique, which provides uniform dispersion and is easy to modify by changing the polymerization conditions. In this method, nanoclays are initially dispersed in monomer solution, then the monomer solution is subjected for subsequent polymerization for producing nanoclay/polymer composite. This polymer composite can also called as hybrid polymer materials, while for metallic nanoparticle/polymer composite production; metallic nanoparticles can be synthesized in situ by using the polymer matrix as the reaction medium. After the clay or metallic particles grafted with thin layer of polymer can be combined with neat polymer matrix to provide desired amount of nanoparticles in final material and secondary processing technique is applied to produce packaging material (Guo et al. 2018).

Tornuk et al. (2018) incorporated the nanoclay particles into LLDPE pellets to produce active nanocomposite films using a twin screw extruder and blown film unit. Huang et al. (2006) added ZnO nanopowder through microinjection molding to investigate the mechanical properties of PP. Lepot et al. (2011) added ZnO nanoparticles without compatibilizer or coupling agent in a PP matrix and investigated its effects on mechanical and barrier properties after biaxial stretching. Zapata et al. (2011) investigated polyethylene nanocomposites containing silver nanoparticles produced via in situ polymerization.

Metallic nanoparticles are also combined on polymer by surface coating method to produce antimicrobial polymer/metal composite coatings. TiO₂ nanoparticles was coated onto OPP film using a bar coater and its antibacterial properties were investigated in vitro and in vivo conditions (Chawengkijwanich and Hayata 2008). Colloidal silver particles have also been coated on paper using ultrasonic radiation, and the coated paper demonstrated antibacterial activity against *E. coli* and *S. aureus* (Gottesman et al. 2011). However, this technique has mainly been used for producing medical instruments, devices and packaging (Cometa et al. 2013; Palza 2015). The coating can be made by using electrochemical or plasma based methods (Fig. 6). Similar to this type technique is used for commercial production of ultrathin SiO_x (protective layer) coated PET bottles. This multilayer packaging material create a barrier for oxygen sensitive foods and carbon dioxide loss from carbonated beverages.

In addition to the above mentioned methods which are widely used for nanocomposite packaging material, some other methods such as electrospinning, sol-gel,

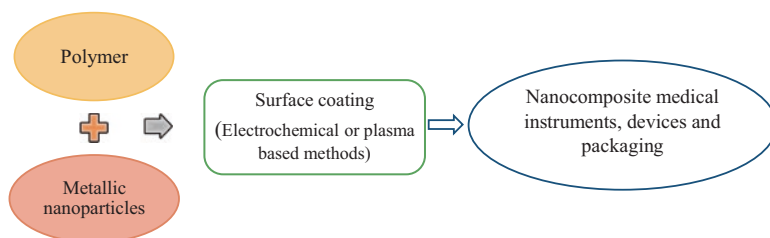


Fig. 6 Surface coating technique

solid-state intercalation have been developed to produce nanocomposites. However, the strict limitations of these methods restrict their wide applications.

Studies on Nanocomposite Food Packaging

Numerous studies and developments about nanoparticle usage in food packaging technology are gaining interest day by day. These studies pointed out that different kind of nanoparticles including metals or metal oxides (silver (Ag), gold (Au), iron (Fe), iridium (Ir), zinc oxide (ZnO), silicon dioxide (SiO₂), titanium dioxide (TiO₂), titanium nitride (TiN), alumina (Al₂O₃), iron oxide (Fe₃O₄, Fe₂O₃), copper (Cu), copper oxide (CuO) and palladium (Pd)) can modify the properties and performance of polymer which was used in packaging. However, commercially most available nanocomposites are based on Ag nanoparticle and nanoclays (Garcia et al. 2018). The results of recent studies about usage of metallic nanoparticles and nanoclays on the polymeric materials are shown in Tables 2 and 3. One of the metallic nanoparticles, titanium dioxide (TiO₂) used in the outer layer of high-density polyethylene bag to decrease the effect of light on carotenoid degradation. Color and astaxanthin degradation was delayed by TiO₂ addition to packaging film (Colín-Chávez et al. 2014). The shrimps packaged in low density polyethylene films containing nano-SiO₂ had better sensory quality and water holding capacity with delayed deterioration, less endoenzyme activity. Nano-SiO₂ using ensured antimicrobial activity and extended the shelf life (approximately 33%) (Luo et al. 2015). Nano-sized metals and their oxide forms are used in food packaging mainly on the purpose of enhancing antimicrobial activity. Inorganic nanoparticles including metallic nanoparticles and nanoclays bind to the cell wall of microorganism and damage it by generating reactive oxygen species. The reactive oxygen species may be responsible for inactivation of proteins, DNA damage and releasing of ions (Hoseinnejad et al. 2018).

Biodegradable nanocomposite films (whey protein isolate/cellulose nanofibre) containing TiO₂ (1%, w/w) reduced the bacterial growth and preserved the sensory qualities of lamb meat. Therefore, edible nanocomposite films with metal oxide nanoparticles are recommended in red meat (Alizadeh Sani et al. 2017).

Table 2 The recent researches about metallic nanoparticles usage

Size	Metal	Matrix	Results	References
Nanosize (rutile)	TiO ₂	HDPE + marigold extract, blown film	Barrier properties against ultraviolet are enhanced; Doubled the shelf life of the carotenoids; Tripled the shelf-life of soybean oil with packaging;	Colín-Chávez et al. (2014)
<250 nm	SiO ₂	Low density polyethylene (LDPE) (titanate crosslinking)	Gas barrier properties were improved; The shelf life of Pacific white shrimp extended	Luo et al. (2015)
Nanosize	Ag	Starch film and/or with a quaternary ammonium salt (clay)	A low concentration of Ag gave antibacterial properties and enhanced clay dispersion Ensure bacteriostatic effect Enhanced the clay dispersion in film Changed the surface polarity	Abreu et al. (2015)
50 nm	SiO ₂	PP (surface treated with EVA)	Oxygen gas and water vapor permeability reduced Tensile strength significantly increased	Li et al. (2016)
50 nm	CuO (1%)	Low density polyethylene (LDPE)	Antimicrobial effect on the growth of coliform bacteria in the cheese	Beigmohammad et al. (2016)
40–60 nm	Ag + TiO ₂ + SiO ₂	LDPE, blown film	Rate of the respiration and ethylene scavenging were lowered; The packaging protected the nutrient content of mushrooms for 14 days	Donglu et al. (2016)
Nanosize (anatase)	TiO ₂ + nanocellulose	Whey protein (added rosemary oil), cast film	Inhibition effect on bacteria Preserved the organoleptic qualities of lamb. The shelf life is extended 9 days.	Alizadeh Sani et al. (2017)

(continued)

Table 2 (continued)

Size	Metal	Matrix	Results	References
40 nm (anatase)	TiO ₂	Low density polyethylene (LDPE)	Developed barrier properties, Lowered O ₂ and increased CO ₂ permeability; Ethylene generation is decreased.	Li et al. (2017)
10–15 nm (anatase and rutile)	TiO ₂	Gelatin/agar, cast bilayer film	Inhibited the oxidation of fish oil.	Vejdan et al. (2017)
20 nm	TiO ₂	PET, bottle	Decreased the permeability of water vapor; Decreased migration of additive from the packaging to a food simulant.	Farhoodi et al. (2017)
<25 nm	ZnO	Chitosan-CMC-oleic acid, cast film	Decreased water vapor permeability; Inhibited microorganisms; Increasing the shelf life of bread to 35 days.	Noshirvani et al. (2017)
60 nm	ZnO	BPAT, cast film	Enhanced mechanical and gas barrier properties; antimicrobial effects	Venkatesan and Rajeswari (2017)
7–9 nm	ZnO + Al,	Coating PLA, extruded film	Antibacterial activity against <i>E. coli</i>	Valerini et al. (2018)
<100 nm	TiO ₂ , TiO ₂ + Ag	PLA, cast film	Antimicrobial effect; Preservation of the freshness; Extended shelf life for cheese to 25 days	Li et al. (2018)
22 nm	ZnO	Biodegradable nanocomposites of cationic starch (CS)	The water vapor permeability and the UV light transmittance are reduced; ΔE* and opacity of the nanocomposites enhanced	Vaezi et al. (2019)

Table 3 shows that montmorillonite, illite and kaolinite are the most used clays in the recent researches. The improvement in tensile strength of the nanocomposite after using a low amount of montmorillonite (MMT) may be relevant with the uniform dispersion of MMT in the matrix, while the decrease in tensile strength in high MMT levels may be caused by aggregation of clay particles (Rostamzad et al.

Table 3 The recent researches about nanoclays

Nanoclay	Matrix	Results	References
A synthetic iron containing kaolinite	HDPE film	The oxygen fighting role of clay: active performance by trapping and reacting with molecular oxygen and a passive barrier performance by imposing a tortuous diffusion path; Relatively inexpensive	Busolo and Lagaron (2012)
Halloysite nanoclay (HNC)	Polysaccharide-based bio-nanocomposite films	Decreased water vapor permeability and oxygen permeability; Increased tensile strength and glass transition temperature Heat seal strength was increased. Elongation at break was decreased. Uniform and smooth surface morphology obtained	Alipoormazandarani et al. (2015)
Montmorillonite (MMT)	Fish myofibrillar protein (FMP) film	Water gain, water vapor permeability and solubility of the film improved; Improved the tensile strength and elongation of nanocomposites.	Rostamzad et al. (2016)
Illite, scoria and hydrotalcite	Nano-biohybrids (nanoclays and antibacterial natural extract)	Nano-biohybrids have higher antibacterial efficacy than extract itself	Kim et al. (2016)
MMT (Cloisite 30B)	Hydroxypropyl methylcellulose (HPMC)-based films	Increased the water barrier; Strengthened the mechanical properties (elastic modulus and tensile strength)	Klangmuang and Sothornvit (2016)
Na ⁺ MMT, HNC and Nanomer®I.44P	Fenugreek seed gum (FSG)/clay nanocomposite films	Improved gas barrier and thermal properties of film; Improved tensile strength properties, Decreased elongation at break values of the film; SEM images showed especially lower levels (up to 5%) of nanoclay reinforcements provided film with smooth structure Water vapour permeability of the films were not improved	Memiş et al. (2017)

(continued)

Table 3 (continued)

Nanoclay	Matrix	Results	References
Na ⁺ MMT	Plasticized banana flour film(PBF)	The lower hydrophilicity of nanoclay improved the water barrier properties	Orsuwan and Sothornvit (2017)
Two different MMT (Cloisite® Na ⁺ ; Cloisite® Ca ²⁺)	Chitosan film	Extending the shelf life of the poultry meat; Reduced lipid oxidation by 50% Reduced microbiological contamination by 6–16%	Pires et al. (2018)
MMT nanoclay	Food-grade edible films with <i>Salvia macrosiphon</i>	Mechanical and thermal properties were considerably improved; The lowest water vapor permeability was obtained in the composite film, Highest elongation at break and tensile strength. Increased the hydrophobicity	Davachi and Shekarabi (2018)
MMT nanoclay	Films of nano-clay-loaded LDPE	Improved thermal and barrier properties; Increased the stability of LDPE; Accelerated the UV oxidation of LDPE	Han et al. (2018)
MMT and HNC	LLDPE based active nanocomposite films with thymol, eugenol and carvacrol	The films had strong in vitro antibacterial activity on pathogens (<i>S. typhimurium</i> , <i>L. monocytogenes</i> , <i>S. aureus</i> , <i>E. coli</i> O157:H7 and <i>B. cereus</i>)	Tornuk et al. (2018)
MMT	Biodegradable nanocomposites of cationic starch (CS)	Reduced the permeability of water vapor and the UV light transmittance	Vaezi et al. (2019)

2016). Nanoclay (modified montmorillonite) increased the water barrier, and also strengthened the mechanical properties of the hydroxypropyl methylcellulose (HPMC) film (Klangmuang and Sothornvit 2016). The thermal resistance increased with the increasing MMT content of the zein based films, while the mechanical and barrier properties changed non-linearly. The properties of the zein nanocomposite films highly affected by the preparation technique of MMT (Luecha et al. 2010).

The migration from package is dependent on the storage time and temperature as well as the morphology of nanocomposites used (Farhoodi et al. 2014). In spite of the results in the literature showed that the mechanical, thermal and barrier properties of the films generally positively affected by nanoclay or metallic particle usage in package; migration studies are considered as insufficient. The lack of studies on

humans and toxicology properties of nanomaterials is of concern about the use of nanotechnology in packaging of foods. Nano-packaging of foods with prior determined and limited health risk and quality changes may enhance the consumer acceptance, food quality and safety appreciably.

Commercial Applications of Nanocomposites

The number of nano-enabled consumer products is increasing rapidly with parallel of manufacturer number. Also, production and distribution of nanotechnology products is increasingly global with the help of shopping malls or over the internet. Although there is a concern about nanotechnology usage in food sector, it has a commercial application in food packaging area. Commercially available packaging materials that contain nanoclay or metallic nanoparticles were listed by many authors (Bumbudsanpharoke and Ko 2015; Drew and Hagen 2016), even the specifications of some products are available on the internet (<http://www.nanotechproject.org/cpi/>). Some examples of commercial nanocomposite packaging materials (nanoclay or metallic nanoparticle) are given below:

- Nanoclay based bottles:
 - Aegis OXCE, (Honeywell International Inc. USA)
 - Imperm Nylon, (Mitsubishi Gas Chemical Company Inc. USA)
- Nanoclay based bags:
 - Debbie Meyer BreadBags (USA)
 - Aisaika Everfresh Bag (Japan)
- Nanosilver based food containers:
 - FresherLonger™ Miracle Food Storage (USA)
 - BlueMoonGoods™ Fresh Box (USA)
 - Nano-silver Storage Box (Baoxianhe) (China)
 - A-DO Global (Korea)
 - Nano Silver NS-315 Water Bottle (A-DO Global, Korea)
 - Nano-silver Salad Bowl (Changmin Chemicals, Korea)
 - Nano Silver Baby Mug Cup (Baby Dream® Co., Ltd.)
- Nanosilver based bag
 - FresherLonger™ Plastic Storage Bags (USA) and
- Nano zinc oxide based film
 - Nano Plastic Wrap (SongSing Nano Technology Co., Ltd. Taiwan) also has been commercialized.

Search on new packaging materials such as increasing the shelf life of food products are still going on. A study on evaluation of the current state of nanocomposite materials research has shown that the USA and the Asian countries are the leaders according to published article numbers and patent applications.

Migration Studies on Nanocomposite Packaging Materials

Migration of substances from packaging materials to food is restricted with a legal regulation. Many countries have developed their own system of regulation, while some countries recognize the regulations of other countries and accept the safety of a packaging material when it complies with such recognized regulations. Responsible authorities related in consumer's health have already been taken measure for consumer protection. Overall migration limit (OML) and specific migration limit (SML) terms are defined for food contact materials including food packaging. The OML has been defined the maximum permitted amount of non-volatile substances released from a material or article into food simulants, SML has been defined as the maximum permitted amount of a substance released from a material or article into food or food simulants in regulations. In many countries, the overall migration limit is accepted as 10 mg/dm² of packaging. This value is also accepted as equal 60 mg/kg of foodstuff, for a cubic package containing 1 kg of food. The SML can be determined according to the acceptable daily intake (ADI) or the tolerable daily intake (TDI) values that are confirmed by the governments or scientific committees on food. In the estimation of SML, it is accepted that a 60 kg person eats 1 kg of packed food that containing the substance in the maximum permitted quantity, every day throughout lifetime.

As mentioned earlier, nanocomposite food packaging is a new generation of packaging technology based on nanomaterials. The use of nanoparticles (metallic and clay) in food packaging materials are developing. The challenges for authorities is that the migration behavior of nanoparticles from the packaging may be different from that of traditional materials, and also migrated nanoparticles may be more reactive and exhibit a different toxicological profile (Rijk and Veraart 2010). Thus, some nanomaterials are not permitted in the EU due to limited available toxicity results (Cushen et al. 2014b).

Migration Tests

Migration tests are an important view of safety evaluation of food packages. According to regulations of many countries any material which will be in contact with food is subjected for migration tests. However, regulations of nanocomposite food packaging materials are limited.

In Europe, a new food packaging material produced from plastic and whether or not contains nanoparticles should be subjected to migration test according to Commission Regulation (EU) No 10/2011. The regulation not only contains SML, but also other restrictions specifically mentioned and it contains specifications related to the substances that possibly migrate to food. Although the best approach is to perform migration test with real food matrices, the determination of migration (especially specific migration value) is analytically difficult and time consuming with the real food (Huang et al. 2015c). To overcome this challenge, the regulations have proposed standardized test conditions (including testing time, temperature and test medium (food simulant)).

Six types of food simulants are introduced and it is mentioned that for determining the appropriate food simulant, the chemical and physical properties of food should be considered.

- Food simulant A (ethanol 10% (v/v)),
- Food simulant B (acetic acid 3% (w/v)),
- Food simulant C (ethanol 20% (v/v)),
- Food simulant D₁ (ethanol 50%),
- Food simulant D₂ (vegetable oil that has a specific fatty acid composition or isooctane),
- Food simulant E (poly(2,6-diphenyl-p-phenylene oxide, particle size 60–80 mesh, pore size 200 nm), respectively.

Food simulants A, B and C represent foods that have a hydrophilic character and are able to extract hydrophilic substances. Food simulant B represents acidic foods which have a pH below 4.5. Food simulant C represents alcoholic foods with an alcohol content of up to 20%, and foods that has slight lipophilic character, while food simulant D₁ represents alcoholic foods with an alcohol content of above 20% and oil in water emulsions. Food simulant D₂ represents foods which contain free fats at the surface. Food simulant E is assigned for represent to dry foods. Also, water is considered as a food simulant represents many food products, such as bread, fresh fruits and vegetables, meat and fish etc., in some countries (Huang et al. 2015c).

In the migration tests, packaging material and food/food simulant are contacted at specific conditions (time and temperature). The contact conditions should be determined according to the intended use of the food package or represent worst foreseeable conditions of using the packaging material (Council Directive 97/48/EC; EC 2011).

Nanoclays and metallic nanoparticles has been used in various polymers (synthetic or biopolymers) and their migration tests have been carried out under different test conditions and medium (food or food simulant). Recent studies on migration of metallic nanoparticles and nanoclay in nanocomposites (NC) are summarized Tables 4 and 5.

Tables 4 and 5 showed the special analytical techniques such as Atomic absorption spectrometry (ASS), inductively coupled plasma mass (ICP-MS), atomic emission (ICP-AES), optical emission spectrometry (ICP-OES), Transmission electron

Table 4 Migration studies on metallic nanoparticles containing nanocomposite food packaging material

Migrant	Polymer type	Food/simulant	Contact conditions	Test method	Result	References
Ag	PVC	Chicken meat	5, 20 °C 1–4 days	ICP-MS	8.85 mg/kg or 0.84 mg/dm ²	Cushen et al. (2013)
Ag	<ul style="list-style-type: none"> • PP based commercial food containers • LDPE based commercial bag 	Water, 3% AA, 10% EtOH, olive oil	20 °C 1 h to 10 days	ICP-MS SEM, TEM-EDX	The migrated silver was detected as ionic form and nanoparticle form. Higher migration level in 3% AA was determined No migration in olive oil	von Goetz et al. (2013)
Ag	<ul style="list-style-type: none"> • Polyolefins based food containers • LDPE based bag 	50% EtOH, 3% AA	40 °C for 10 days 70 °C for 2 h (three cycles)	ICP-MS, SEM-EDX	Migration was higher in AA. Migration values were much higher when heating in a microwave oven than in a conventional oven	Echegoyen and Nerin (2013)
Ag, Cu	PE	Chicken breasts	8, 13–21.8 °C 1, 1–3, 1 days	ICP-MS	Effects of time and temperature on the migration were not significant	Cushen et al. (2014a)
Ag	PE	Water, 3% AA	40 °C 10 days	ICP-AES, TEM	The initial amount of Ag and simulant type were significant effect on migration rate.	Cushen et al. (2014b)
TiO ₂	PE	3% AA, 50% EtOH	25, 70, 100 °C 1–8 h	ICP-MS, LPSPA	The maximum migration amounts into AA was 12.1 ± 0.2 µg kg ⁻¹ , while into EtOH was 2.1 ± 0.1 µg kg ⁻¹ at 100 °C. Increasing additives in the film increased migration. The researchers noted that cut edges of the film can be contribute to migration.	Lin et al. (2014)
ZnO+ Ag	LDPE	Water	40 °C 10 days	ICP-MS	ZnO migration more than Ag migration.	Panea et al. (2014)

(continued)

Table 4 (continued)

Migrant	Polymer type	Food/simulant	Contact conditions	Test method	Result	References
Ag	Commercial PP based containers and LDPE based bags	W, 3% AA, 10% EtOH, 95% EtOH	10 days at 20 °C, 10 days at 40 °C, 2 h at 70 °C	ICP-MS, AF4-ICP-MSSEM-EDX	Silver ions and nanoparticles were distinguished during migration tests. Chlorine and sulphur atoms could play a role on AgNPs transformations during migration test	Artiaga et al. (2015)
Ag	Commercial PE containers and Commercial PE cling film withcoated silver	Bread, Apple, Cheese, Milk powder; Orange juice, Carrot, Ground beef, Butter/W, 3% AA	40 °C 7–10 days	AAS, ICP-MS	Too low levels of Ag were released from containers into real food samples and food simulants. While, higher levels of migration have been detected for samples exposed to nano-silver coated films. No chemical or biochemical changes observed for the food samples.	Metak et al. (2015)
Ag	PE based commercial containers, HDPE based commercial bag PE based commercial bag	W, 3% AA, 10% EtOH	40 °C 10 days	ICP-MS, sp-ICP-MS, TEM, EDS	The total content of silver in the containers varied from 13 to 42 µg/g. The highest total Ag migration was observed for AA (3.1 ng/cm ² after 10 days) Nanoparticle release was observed for all food container brands. The released particles were detected as spherical particle.	Mackevica et al. (2016)
Ag	PP based containers, dishes, cups, cutting boards PE based bags	W, 4% AA, 20% EtOH	10 days at 5 °C 10 days at 40 °C 30 min at 60 °C 30 min at 95 °C	ICP-MS Ultrafiltration	Migrations of Ag and Zn were highest in AA. The Ag that migrated from nanosilver products into AA was in the ionic form, and those into W and EtOH were in the nanoparticle form.	Ozaki et al. (2016)

ZnO	PE based film	3% AA, 10% EtOH, isooctane	10 days at 40 °C 2 days at 20 °C	AAS with graphite furnace	Films containing 3% or more ZnO nanoparticles were determined inappropriate for packaging of acidic foods.	Polat et al. (2018a)
ZnO	PP based film	3% AA, 10% EtOH, isooctane	10 days at 40 °C 2 days at 20 °C	AAS with graphite furnace	Migration values were changed depending on initial concentration of ZnO Max migration value was detected as 14.06 mg/kg in AA.	Polat et al. (2018b)
ZnO	PP based films	3% AA	40 days at 20 °C 25 days at 40 °C 24 days at 70 °C	ICP-AES	Three types of polypropylene nanocomposite films with or without coupling agent were tested. The coupling agent decreased migration. The higher migration rate was detected for homopolymer of polypropylene.	Chen and Hu (2018)

Table 5 Migration studies on nanoclay containing packaging materials

Migrant	Polymer type	Food/simulant	Contact conditions	Test method	Result	References
Cloisite 20A	PET bottles	3% AA	90 days at 45 °C	ICP-OES	Migration was increased with storage time and temperature. Aluminum migration was detected as 0.34 mg/kg Silicon was detected as 9.5 mg/kg	Farhoodi et al. (2014)
MMT	BOPP/nanocomposite-adhesive/BOPP Multilayer film	W, 3% AA, 15% EtOH, olive oil, grapeseed oil and coconut oil	20, 25, 40, 70 °C 2, 6 h 1, 3, 7, 10 days	ICP-OES	The migration of Si increased with storage time and temperature Migration was higher in AA. They suggested a numerical model based on Fick's diffusion theory.	Huang et al. (2015b)
Nanoclay	Commercial LDPE based bags	10% EtOH 3% AA	10 days at 40 °C 2 h at 70 °C	ICP-MS	Aluminum migration was observed for both samples 51.65 ng.cm ⁻² for the Aisaika brand 24.14 ng.cm ⁻² for the Debbie Meyer bag	Echegoyen et al. (2016)
Cetylpyridinium bromide (CPB)-modified MMT	LDPE	10% EtOH	35 day	Electrical conductivity	The organoclay surfactant migration was detected. The migration increased with time.	Muñoz-Shugulí et al. (2019)

microscopy (TEM), Laser particle size analysis (LPSA), energy dispersive X-ray spectroscopy (EDS), Ultrafiltration can be used for the determination of nanoparticles migration. These techniques are different from common chromatographic techniques applicable to conventional polymer additives. The chromatographic techniques are inappropriate or severely limited because they cannot measure particle size, shape and aggregation of nanoclay or metallic nanoparticles. Because of its high selectivity and sensitivity, ICP-MS is more favored than ICP-OES and ICP-AES in migration studies of nanoparticles. However, basic ICP-MS does not differentiate between nanosized elemental metal and metal ions, which in case of nanosilver migration studies means dissolved silver ions and dispersed silver in its particulate form. Single particle (sp) ICP-MS is recommended as a new technique able to distinguish quantitatively between dissolved and particulate species. However, the sp-ICP-MS technique has also not respond fully to detect metal and metal ions quantitatively in some nanoparticle migration studies. Because, metal species can be changed reversibly the oxidation state from metal to metal ions by the chemical environment. Such a redox change may also be occurred when handling and concentrating migration solution for preparation to TEM measurement. So, extreme care needs to be taken when preparing the samples for the analytical techniques which are used for migration tests (Störmer et al. 2017).

Ozaki et al. (2016) investigated the migration of silver from food-contact plastics, six nanosilver-labelled products and five silver ion (Ag^+) labelled products, to various food simulants (water, 4% acetic acid, 20% ethanol). They detected highest Ag and Zn migration values in 4% acetic acid. With the increase of migration time and temperature, the release of Ag and Zn increased. Moreover, they observed that the Ag migrated from nanosilver products into the acetic acid was in the ionic form, and those into the water and 20% EtOH were in the nanoparticle form. Chen and Hu (2018) studied ZnO migration from three types of polypropylene (homopolymer (PPH), block copolymer (PPB) and random copolymer (PPR) of polypropylene) nanocomposite films with or without coupling agent to 3% acetic acid and reported addition of the coupling agent could decrease ZnO migration, because the coupling agent could improve the interface between ZnO and PP molecular chain segment. Moreover, the migration rate of ZnO changed depending on the degree of crystallinity of polypropylene and higher migration values were detected for PPH, PPB and PP, respectively.

Studies demonstrated that migration of nanoparticles from food packaging material into food or food simulants may be changed by multiple factors including temperature, time, the initial concentration of nanoparticle in polymer matrix, polymer properties, position of the nanoparticles in the packaging material, interaction between the nanoparticles and the materials, sampling type of material, contact type of material and the nature of the food/food simulants. Generally, the nanoparticles have the potential of migrating into food, especially when in contact with more acidic substances. Studies also showed that sampling method of packaging materials and contact type has an effect on migration values, because sampling of the material (cut edges) may create new surface areas for migration.

According to migration studies, it can be concluded that there is no standard techniques for the detection and characterization of nanoparticles migrated from polymer matrices to foods. Thus, the different techniques should be used with a proper sampling method that allows sensitive chemical detection and quantification as well as accurate physical determination of particle sizes, and also distinguish between dissolved and particulate nanomaterials even in complex matrices.

As a summary the challenges in migration studies are;

- There are no standard test conditions for nanocomposite materials
- Authorizations of a material in its bulk form do not imply authorization of the nanoform (especially for metallic nanoparticles)
- Current migration limits do not apply to nanoparticles
- There are difficulties for detection of metallic nanoparticles migration with the current analytical methods

Health Aspects of Inorganic Nanoparticles

Consumer safety has become a serious concern, because of the increasing interest in the use of nanoparticle based products. Nanoparticles may have differential toxicity, because they have different physicochemical properties, such as chemical, optical, magnetic, and structural. Even in cases where nanoparticles do not show any acute toxicity, questions of long-term effects remain unanswered on bioaccumulation and in food chains (Tiede et al. 2008). Therefore, the generalization of potential toxicological effects of nanomaterial-based products are extremely difficult (Vega-Villa et al. 2008). The type of nanoparticles and related chemical, physical, and morphological properties affect their interaction with living cells. Moreover, they determine the route of clearance from the gastrointestinal system and possible toxic effects (Borel and Sabliov 2014). Nanoparticles bio-distribution occurs through systemic circulation to organs such as liver, kidneys, spleen, heart, lungs, and brain. The biotransformation of the nanoparticles occurs through interactions with proteins and lipids in tissues such as the liver and intestine (Vega-Villa et al. 2008). It is known that the liver, kidneys, and colon are primarily responsible for excretion of nanoparticles and their possible metabolites (Bertrand and Leroux 2012; Bouwmeester et al. 2009).

Several research groups around the world started to probe potential toxicological effect of nanoparticles on human health and biological systems. The evidences collected from the studies have shown that there are reasons to suspect that nanoparticles may have potential toxic effect on biological systems (Bouwmeester et al. 2009). Clinical and experimental studies showed that reactive oxygen species can be catalyzed by nanoparticles and thus, causing oxidative stress and subsequent inflammation by the aid of interaction with the reticulo-endothelial system (Nel et al. 2006). Lordan et al. (2011) conducted the cytotoxicity of two different nanoclays (the unmodified (cloisite-Na⁺) and organically modified (cloisite-93A)) in

human hepatoma cells frequently used as *in vitro* alternatives to primary human hepatocytes. The results showed that cloisite- Na^+ induced intracellular reactive oxygen species (ROS) formation which coincided with increased cell membrane damage, while ROS generation did not play a role in cloisite-93A-induced cell death due to low accumulation in the cell culture. In addition, the nanoclays aggregated differently in the cell culture medium and appeared to have an effect on their mechanisms of toxicity. They concluded that the studied nanoclays are highly cytotoxic, and therefore pose a possible risk to human health. Finally, they suggested that the effect of size, shape, composition and aggregation-dependent interactions of nanoclays on biological systems with particular attention given to food packaging applications to be studied.

The effects of Nano-silver particles (Ag-NPs) on traits of productivity, oxidative stress and some of important blood parameters in broiler chicks was conducted by Ahmadi (2012). The findings indicated that no significance in growth performance of the chicks was detected, while significant change was found in the feed efficiency. The blood parameters such as ALT, AST, ALP, TP, albumin, gamma globulin, triglyceride, and cholesterol were significantly changed in the exposed broiler chicks. Another interesting result was on oxidative stress enzymes responsible from production of reactive oxygen species have been reported. These enzyme activities increased significantly in nano-silver exposed chicks when compared to untreated samples. Arora et al. (2009) used primary liver and fibroblasts cells that were suitable for *in vitro* toxicity studies in order to determine interactions of silver nanoparticles. They indicated that morphology of primary liver and fibroblasts cells remained unchanged up to 100 $\mu\text{g}/\text{mL}$ and 25 $\mu\text{g}/\text{mL}$, respectively. The antioxidant defense mechanisms were also probed in terms of lipid peroxidation levels, concentration of glutathione (GSH) which is responsible from reducing damage effect of oxidative stress in cell and finally, superoxide dismutase activity (SOD) catalyzing superoxide radicals into molecular oxygen or hydrogen peroxide. The effect of different doses and sizes of nano-silver particles, as well as biocompatible coating on the proliferation of mouse germline cells was carried out in a research study by Braydich-Stolle et al. (2010). According to the results, reduction in proliferation of the cells treated with any type particles was not observed for exposure lower than 10 $\mu\text{g}/\text{mL}$ and also these concentration levels did not appear to be stressed the cells, because there was not detection of ROS production or any signs about cell apoptosis. However, significant decrease in cell proliferation was observed for the exposure higher than 10 $\mu\text{g}/\text{mL}$ after 24 h incubation. Moreover, particle size and type of coating affected significantly this mechanism; especially smaller particles caused greater decrease than larger ones. Hackenberg et al. (2011) evaluated possible toxicological effect of Ag-NPs on human cells. They exposed the human cells in solution having concentrations of 0.1, 1 and 10 $\mu\text{g}/\text{mL}$ for 1, 3, and 24 h and showed that significant change was found for cell DNA treated with higher Ag-NPs and longer treatment time. Huang et al. (2015a) treated the mouse brain neural cells with 3–5 nm Ag-NPs to investigate whether these particles can pass through the cells and biochemical responses of the cells were monitored. Their results showed that 3–5 nm Ag-NPs are able to cross the cell membrane, which induced the gene expres-

sion related with inflammatory process and phagocytosis. Moreover, in Ag-NPs exposed cells, stress-responsive gene and immune reaction genes were activated. Taken into consideration of all findings obtained from the mouse brain cells exposed with Ag-NPs, the researchers concluded that the progress of neurodegenerative disorders might evolve due to induced neuroinflammatory response and amyloid ($A\beta$) deposition. Moreover, the researchers highlighted that it is necessary to figure out the daily usage and distribution of Ag-NPs in the environment with future studies.

In the food industry, TiO_2 -NPs are commonly used due to anticaking properties or antimicrobial effects (Smolkova et al. 2015). The experimental studies generally indicated that DNA damages (as oxidation or breaks) were determined in the cells exposed with TiO_2 -NPs (Magdolenova et al. 2014). The particle size of TiO_2 in agglomerates showed different toxicity in human or animal cells. The results indicated that no genotoxic effect was detected for the cells treated with TiO_2 -NPs dispersed with agglomerates less than 200 nm, while larger agglomerates caused DNA damages in the exposed cells (Magdolenova et al. 2012). Kreyling et al. (2017) injected aqueous suspension of TiO_2 -NPs agglomerated with size of 70 nm for conducting bio-kinetics of the nanomaterials in rats. The bio-kinetics of TiO_2 -NPs were investigated in liver, spleen, kidneys, lungs, heart, brain, uterus, blood, carcass, skeleton, and soft tissue and the exposed rats were also monitored from one-hour to 4-weeks in terms of TiO_2 -NPs accumulation. They reported that TiO_2 -NPs were in detectable level for all studied organs. After 24 h, the highest accumulations of TiO_2 -NPs were determined in liver with 95.5%, followed by spleen with 2.5%, carcass with 1%, skeleton with 0.7% and blood with 0.4%. The findings showed that the concentration of TiO_2 -NPs reduced remarkably in blood after 24 h from the exposure, while the distribution showed constant tendency until 28 days in other organs and tissues. In another study, 15 post-mortem humans were surveyed to present TiO_2 -NPs accumulation in livers and spleens. The results showed that the nanoparticle counts in liver and spleen ranged from 1×10^9 to 21×10^9 TiO_2 -NPs/kg tissue and from 1.2×10^9 to 56×10^9 TiO_2 -NPs/kg tissue, respectively. In addition, at least 24% of TiO_2 -NPs detected in the organs were smaller than 100 nm (Heringa et al. 2018). Sycheva et al. (2011) studied genotoxic and cytotoxic effects of TiO_2 on in vivo mice treated orally with the size of micro- (160 nm) and nanoparticles (33 nm) in dose of 40–1000 mg/kg bw. The circulation of TiO_2 particles was also followed in the cells of six organs, namely; liver, brain, bone marrow, colon, testis and for stomach. The results showed that the micro- TiO_2 induced DNA damage and micronuclei in treated bone marrow cells, while nano- TiO_2 induced DNA damages both liver and bone marrow cells. Moreover, a significant reduction was determined in sperm count and function of mice treated with high-dose TiO_2 . They explained these undesirable effects with genotoxic and cytotoxic mechanisms related with inflammation or oxidative stress caused by TiO_2 particles in the exposed cells and highlighted that over exposure of TiO_2 particles has a potential health risks and dose-dependent studies must be conducted to determine acceptable daily exposure of micro- or nano-scale of TiO_2 particles.

The toxicological effect of Zn-NPs at different concentrations (500 μ g/L and 2000 μ g/L) on the fish brains were studied by Saddick et al. (2017). The exposed

fish results showed that there are significant increases in the enzymes activity associated with antioxidant mechanism. Moreover, for treated fishes, 96 h lethal concentrations (LC_{50}) of Zn-NPs were calculated as between 5.5 and 5.6 mg/L. The effects of zinc-copper alloy nanoparticles (Zn/Cu-A-NPs) on human lung cells were investigated with in vitro study in terms of cyto- and genotoxicity. They reported that the exposure of Zn/Cu-A-NPs caused significant DNA damages in the lung cells and presence of Zn/Cu-A-NPs in the medium induced significant formation of intracellular reactive oxygen species. Due to potential toxic effect of Zn/Cu-A-NPs on the biological systems (Kumbıçak et al. 2014). Lanone et al. (2009) conducted a comparative study about the toxicity of 24 nanoparticles that are of equivalent spherical diameter and different elemental compositions using various cytotoxicity assays. They used different cells originated from human tissue in order to investigate toxicity of the nanoparticles. Their results demonstrated that the highest toxicity responses were from cells exposed to Cu- and Zn-based nanoparticles, while the moderate toxicity responses were obtained for cells treated with Ti-, Al-, Ce and Zr-based nanoparticles. However, no detectable toxicity was determined for tungsten carbide nanoparticles. The researchers also stated that there is no significant correlation between equivalent spherical diameter or specific surface area of nanoparticles and cytotoxicity. They concluded that choosing of cytotoxicity assays and cell types, due to different sensitivities, are very important points to be clearly put forth possible toxicity effect of nanoparticles. Wang et al. (2016) demonstrated the possible effects of diets containing ZnO-NPs between 0–5000 mg/kg on growing mice, Zn metabolism and biodistribution. They fed the mice with ZnO-NPs and change in the metabolism was monitored during 34 weeks. The biodistribution findings showed that a significant accumulation was detected in kidney, bones, liver and pancreas of mice fed with 5000 mg/kg ZnO-NPs. However, exposing ZnO-NPs between 50–500 mg/kg in the diets for long term showed minimal toxicity in the mice. As a result of long term exposure (34 weeks), the lowest body weight was determined for the mice exposed with diet of 5000 mg/kg ZnO-NPs. Moreover, in the mice treated with the same diet concentration, the relative weights of lung, brain and pancreas increased significantly. Compared to untreated mice, expression of mRNA associated with Zn metabolism induced significantly in mice receiving 5000 mg/kg ZnO-NPs.

Conclusion

In spite of the toxicological properties of inorganic nanoparticles, the research studies on nanocomposite food packaging materials and number of commercial food contact materials containing inorganic nanoparticles are in continuous extension. According to the research results, the positive effects of inorganic nanoparticles on the properties of food packaging materials are incontrovertible. However, the migration features of these nanoparticles are a matter of debate. Some of the migration studies performed on food simulants showed that the migration values of nanocom-

posite materials are lower than the detection limits of the analysis technique although an exposure risk to these nanoparticles still suspected by other studies with an ambiguity related to the toxicological form of these particles. Thus, specific migration limits of each inorganic nanoparticle should be set up in addition to the improvement of the test method sensitivity in order to overcome to these weaknesses. Finally, to deal with the expected increase of using nanocomposites in food contact material the governments and independent associations are forced to design urgently science-based regulations.

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