

# Chapter 7

## Green and Bio-Mechanochemical Approach to Silver Nanoparticles Synthesis, Characterization and Antibacterial Potential



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**Abstract** The area of nanotechnology has been enjoying enormous research interest recently because of the unique characteristics of nanoscale substances. Silver nanoparticles (AgNPs) are attractive for their broad spectrum of utilization in various sectors. Among the several ways of AgNPs preparation, we focused on green synthesis using phytochemicals present in plants without the use of chemicals and surfactants that are harmful for humans and environment. In this chapter, we provide a comprehensive review of the various options of green preparation of silver nanoparticles including bio-mechanochemical synthesis. Just few reports on the bio-mechanochemical synthesis combining tools of mechanochemistry (ball milling) and of green synthesis (plant material) were reported until now, and these studies are briefly reviewed. They show green and sustainable character of this method and underline the growing interest of scientists towards mechanochemistry. Silver and its compounds are known as strong antibacterial agents, so we have focused on description of the methods frequently applied to determine the antimicrobial properties of AgNPs.

**Keyword** Silver nanoparticles (AgNPs) · antibacterial activity · mechanochemistry · plant extract · green synthesis

## 7.1 Introduction

Due to small particle size, various shapes and high surface areas, silver nanoparticles show different chemical, physical and biological properties and lead to the broad spectrum of their applications in pharmaceutical field, catalysis, sensors, spectroscopy or electronics (Abbasi et al. 2016; Prasad et al. 2016). Silver provides activity against many bacterial species, so it is commonly used in medical industry, including creams with silver content to avoid local infections after open wounds or burns, soaps, catheters, pastes and textiles (Becker 1999; Catauro et al. 2004; Dallas et al. 2011; García-Barrasa et al. 2011).

Preparation of AgNPs can be realized by various ways. In general, we can classify these techniques as chemical, biological and physical. Some of these techniques are simple with good nanoparticle size control and can be achieved by affecting the process of reaction, but on the other hand, there are some difficulties and complications with stability of the products (Kowshik et al. 2002). Despite that, many of the reactants and surfactants engaged in these processes are dangerous to human health and the environment, and so, a “green” approach for metal nanoparticles is necessary.

Methods of classical chemical or physical approach to nanoparticles synthesis are environmentally toxic and economically demanding (Kalaiarasi et al. 2013). These objectives have forced the scientific community to search for new, easy and environmentally friendly choice that would not be harmful for humans, animals and environment. These facts shifted the attempts to synthesize Ag nanoparticles using green synthesis methods that have been indicated to be easy, economically advantageous and environmentally friendly (Prasad 2014). The green preparation of silver nanoparticles means preparing nanoparticles using biological routes for Ag(I) ion reduction by natural sources of reducing agents. These sources include microorganisms (algae, yeast, fungi, bacteria), plants and plant extracts or their products, such as small biomolecules including vitamins, amino acids or polysaccharides (Sharma et al. 2009; Ahmed et al. 2016; Mohammadlou et al. 2016; Prasad et al. 2016, 2018). Nanoparticles prepared by green approach are much superior to nanoparticles prepared by chemical and physical processes, as green methods exclude the use of toxic and consumptive chemicals and save the energy needed for synthesis (Clark et al. 2002; Kharissova et al. 2013; Prasad et al. 2016).

Nowadays, investigation on nanometals' biosynthesis by plant extracts has become immensely popular. This alternative green approach to the synthesis of AgNPs, which utilizes plant sources in the synthesis of metal nanoparticles, has developed in the new area of "phytonanotechnology" (Rajan et al. 2015; Prasad 2019). This method reflects the newest epoch in rapid and harmless methods for nanoparticles synthesis. For that reason, the present work has focused on silver nanoparticles synthesis using plant extracts. As already mentioned before, there are several ways of silver nanoparticles preparation. Among them, an environmentally friendly solvent-free approach called mechanochemistry has been used. However, the reports on bio-mechanochemical synthesis (co-milling of plant material and silver nitrate) are rather scarce (Rak et al. 2016; Arancon et al. 2017; Baláž et al. 2017a, b).

This chapter provides a brief introduction into the topic of green synthesis of silver NPs, outlining the most important group of compounds responsible for reduction, commonly used characterization techniques and methods used for antibacterial activity determination. The second part is devoted to the bio-mechanochemical preparation of silver NPs.

## 7.2 Green Synthesis of Silver Nanoparticles

The term "green chemistry" is generally understood as a principle to reduce chemistry-related impacts on human health and to eliminate the environmental pollution. Green chemistry represents a different way of thinking how chemistry can be done, for example, by reducing waste, saving energy, using non-toxic chemicals and solvents (de Marco et al. 2018; Joshi et al. 2018).

Nature is an endless source of compounds which can be used for silver nanoparticles synthesis by green chemistry approach. Synthetic methods using biomaterials are in line with the principles of "green" chemistry, as safe and non-toxic reagents

are used to prepare nanoparticles. This part of the chapter is focused on green approach for the Ag nanoparticles synthesis using plant extracts. These procedures are performed outside of a living organism using an extract without cells producing reducing molecules with reducing capacity.

Green approach to nanoparticles synthesis is based on bottom-up approach, where the reducing agents contained in plants are liable for the Ag(I) ion bioreduction to prepare AgNPs. This process starts after incubation of the plant extracts with silver salts (silver nitrate is mostly used). In general, the biosynthesis of Ag nanoparticles involves three steps. The first is an induction step involving the reduction of Ag(I) ions followed by the second phase of growth, where larger aggregates are produced, and finally, the third, stabilizing step, in which the stabilization of prepared nanoparticles is carried out (Marchiol et al. 2014). The green approaches include the choice of suitable solvent used for the Ag nanoparticles synthesis and the choice of environmentally friendly reducing agent and non-toxic material as a capping agent for nanoparticle stabilization. The green reduction of silver ion is completed by natural material, mainly extracts obtained from plants, which contain reducing compounds, for example phenolics, flavonoids, terpenoids or saccharides (Prabhu and Poulose 2012), which also are responsible for their stabilization. In the plant-mediated nanotechnology field, a variety of plant parts (flowers, fruit, leaves, root, stem, seed, peel) are used (Kharissova et al. 2013; Mittal et al. 2013; Ahmed et al. 2016; Carmona et al. 2017).

In the concept of green approach of AgNPs synthesis, elimination of the use of toxic chemical is expected. Extractable phytochemicals therefore play a dual role as both reducing and stabilizing representatives for the production of metal nanoparticles containing AgNPs simultaneously without any involvement of chemicals. This approach is dependent on the amount of reductants contained in the extract, and therefore, the key step is to extract these *reductants* and *capping agents*.

### 7.2.1 Extraction

The ways of efficient extraction of the bioactive compounds were intensively studied in literature (Azwanida 2015). Several techniques have been studied to optimize the extraction process of these compounds, such as drying methods, temperature of extraction and extraction solvent type. Extraction of different plant parts can be done by several extraction procedures. The initial stage in the plant extract production is the preparation of plant samples. Different parts of plants such as leaves (Ajitha et al. 2015; Khatoon et al. 2018), barks (Velayutham et al. 2013), roots (Behravan et al. 2019), fruits and flowers can be extracted from fresh or dried plant material prior to AgNPs synthesis. Generally, after the collection of plant/plant parts, the cleaning of plant material by washing it twice or more times with distilled water follows. Both, fresh and dried plant samples are used in plant extract preparation. After drying procedure, the plants are powdered or ground. Lowering the particle size allows better contact between sample and extraction solvent.

The solvent types used in the extraction importantly influence the quantity of the extracting reducing agents. The most frequently used solvent for extraction of bio-reducing compound is water. There are few reports regarding the use of organic solvents for extraction, like *Murraya koenigii* methanol leaf extract (Suganya et al. 2013), *Ziziphora tenuior* methanol extract (Sadeghi and Gholamhoseinpoor 2015), *Malva parviflora* ethanol/water extract (Zayed et al. 2012). In most cases, the solvent was evaporated and the residue diluted in water for silver nanoparticles synthesis.

Traditional solvent extractions of biologically active compounds from plant raw material are carried out in aqueous solution or organic solvents and by application of heat and mixing. The most frequently used traditional methods include soxhlet extraction (Sadeghi and Gholamhoseinpoor 2015), maceration (Zayed et al. 2012), percolation (Padalia et al. 2015) and sonication.

Instead of conventional extraction techniques, several modern extraction techniques were developed. Mechanochemical-assisted extraction (MCAE) belongs to the innovative pre-extraction techniques (Wu et al. 2017), the forming of which is nearly connected with the development of mechanochemistry (Baláz et al. 2013). This method has been established and put in an application for the bioactive compounds' extraction. In addition to the extraction method of heat reflux, the method of MCAE has higher yield of extraction, shortened time of extraction and lower temperature of extraction, so it can decrease or evade the reduction of thermolabile compounds' amount. MCAE's main goal is mechanical treatment of powder mixtures of plant materials and suitable reagents in special mill activators to solubilize the biologically active compounds (Lomovsky et al. 2017). In general, the MCAE procedures involve three steps, including sample preparation, mechanochemical treatment of plant material with solid reagent in ball mill and subsequent extraction procedure. There are several ways how MCAE provides improvement of extractable biomolecules: (a) the particle size reduction leading to the total contact surface area increase, so the probability of the reaction of biologically active compounds with the solid agents increases; (b) cell wall damage; and (c) chemical form transformation. The MCAE also allows the chemical conversion of compounds to enhance the solubility in water, so water can be used as a solvent of extraction as an alternative to organic solvents (Wu et al. 2017). This method was used for improved extraction, for example flavonoids from bamboo (Xie et al. 2013), chondroitin sulphate from shark cartilage (Wang and Tang 2009), polysaccharides extraction from *Ganoderma lucidum* spores (Zhu et al. 2012) or alkaloids from *Stephania tetrandra*, *Stephania moore* (Wang et al. 2019).

Plant extracts can be also obtained via microwave-assisted extraction (MAE). The MAE is a versatile technique which offers lower extraction period, higher extraction yield and less energy consumption. In addition, the microwave oven produces high temperature, which facilitates the breakage of the cell wall when the plant material is extracted, and as a result, active substances extraction is facilitated in the solvent. Water can be used in MAE under controlled temperatures. Different plants were subjected to MAE prior to AgNPs synthesis like red cabbage (Demirbas

et al. 2016), green tea (Sökmen et al. 2017) and *Anthriscus cerefolium* (L.) Hoffm. (*Apiaceae*) (Ortan et al. 2015).

Safarpour used ultrasound-assisted extraction (UAE) of 40 kHz frequency for preparation of *Thymus daenensis* and *Silybum marianum* ethanolic extract prior to AgNPs synthesis. (Safarpour et al. 2018). Ultrasound-assisted extraction by effect of acoustic cavitation from the ultrasound facilitates inorganic and organic substances leaching from plant matrix. The extraction mechanism can be described by the diffusion through the cell wall and washing the contents of cell after destruction of the cell walls. The procedure is simple to use and relatively cheap that facilitates release of compounds. The UAE or sonification can be advantageously used for shortening the extraction time and extraction of termolabile biological compounds (Azmir et al. 2013; Azwanida 2015).

## 7.2.2 *Biomolecules with Reducing Ability*

The green synthesis of nanoparticles is based on the bioactive compounds extracted from plants that are able to reduce the metal ions to their elemental form. These metabolites are from group of terpenoids, flavonoids, tannins, phenolic acids, saponins, steroids, alkaloids, saccharides, proteins, amino acids, enzymes or vitamins (Kulkarni and Muddapur 2014). The mentioned substances containing reducing groups (OH, CH=O, NH<sub>2</sub>, SH) are able to reduce silver ions to the elementary form Ag(0) and produce the Ag nanoparticles, but also play an important role in their stability. Metal nanoparticles prepared by plant extracts were found to be functionalized with biomolecules that have primary amino, carbonyl, hydroxyl or other stabilizing functional groups (Kulkarni and Muddapur 2014; Sadeghi and Gholamhoseinpoor 2015). Different concentrations and ratio of active compound in plant have effect on the morphological diversity of nanoparticles (triangles, cubes, spherical, ellipsoids and others) and their properties (Makarov et al. 2014).

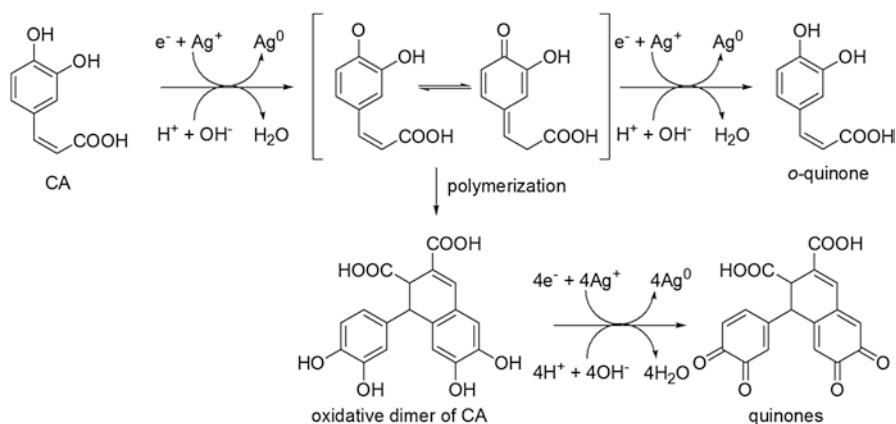
### 7.2.2.1 *Flavonoids*

Flavonoids represent a wide group of plant secondary phenolic compounds based on the flavan nucleus and can be divided into isoflavonoids, flavonols, flavones, flavanones, chalcones and anthocyanins (Kelly et al. 2002). The number, positions and types of substitutions influence the preparation and stabilization of nanoparticles. Tautomeric transformation of enol-form of flavonoid molecule to its oxo-form is responsible for the synthesis of nanoparticles, because it may release hydrogen which can reduce metal ions to NPs. For example; it is predicted that luteolin and rosmarinic acid present in *Ocimum basilicum* are responsible for AgNPs formation from silver ions by changing their tautomeric forms (Ahmad et al. 2010). Dihydromyricetin-mediated silver nanoparticles were synthesized by green way

from  $\text{AgNO}_3$  and flavonoid dihydromyricetin (also known as ampelopsin) isolated from *Ampelopsis grossedentata*. Hydroxyl and carbonyl groups of dihydromyricetin were involved in formation of spherical Ag nanoparticles (Ameen et al. 2018).

### 7.2.2.2 Terpenoids

Terpenoids are secondary plant metabolites constructed from two or more isoprene units. Silver nanoparticles were prepared, for example, by rapid biosynthesis using leaf extract of *Thuja occidentalis* (Kanawaria et al. 2018). The nanoparticles were also encapsulated and stabilized by organic layer which contains mainly terpenes and terpenoids. These secondary metabolites take a part in preparation of nanoparticles and in their stabilization; it means prevention of agglomeration (Kanawaria et al. 2018). The main secondary metabolites from leaf extracts of *Azadirachta indica* (flavonoids and terpenoids) act as a reducing agent for the preparation of silver nanoparticles from  $\text{AgNO}_3$  and also as a capping agent (Roy et al. 2017). Ag nanoparticles were prepared in a very short time using clove extract. The main constituent of clove extract is terpenoid eugenol which is responsible for bioreduction of metallic ions to nanoparticles. The mechanism of bioreduction via eugenol terpenoid found in the clove has been described. The induction effect is mediated by methoxy and allyl groups, which are located in the eugenol structure in the *para* and *ortho* positions to the  $-\text{OH}$  group capable of releasing the proton, thereby forming a resonance-stabilized anionic form. It is then able to release two electrons from one eugenol molecule (Singh et al. 2010).



**Fig. 7.1** Supposed mechanism of the AgNPs formation using caffeic acid in rice husk extract (Liu et al. 2018)

### 7.2.2.3 Phenolic Acids

High nucleophilicity of aromatic ring may support the chelating ability. Phenolic acids containing hydroxyl and carbonyl groups are considered as the major phytochemicals. For example, in rice husk, phenolic acids were investigated for their reducing ability to Ag(0) ion. An alkaline medium fits the transfer of the electron from the phenolic acids to reduce Ag(I) to create AgNPs, and in Fig. 7.1, the proposed mechanism for generating AgNPs prepared by caffeic acid (CA) in the rice husk extracts is shown. The reduction process of Ag(I) includes releasing of electrons to reduce Ag(I) to Ag(0), form caffeic acid-derived free radical, and consequently, another Ag(I) is reduced and CA is oxidized to *o*-quinone. Additionally, a caffeic acid dimer is produced which provides four electrons for Ag(I) reduction and is oxidized itself to quinone form (Fig. 7.1). The quinone derivatives can be combined to create a steric hindrance around the AgNPs, which avoids aggregation and enhances the stability of NPs (Liu et al. 2018).

### 7.2.2.4 Saccharides

One of the biomolecules used as bioreducing agents are saccharides. Saccharides represent a wide group of polyhydroxy derivatives. The reducing ability of saccharides depends on two factors. The first is the content of individual monosaccharides and the second is binding between them. Saccharides that are used for synthesis of nanoparticles have many advantages; (a) availability, (b) low price (c) environmental reasons (d) capping ability (Panigrahi et al. 2004).

Glucose is supposed to be a strong reducing agent than fructose. However, it was found that fructose is better for synthesis of smaller nanoparticles and hence utilized for the preparation of Au–AgNPs composite (Au-core, Ag-shell) of ~10 nm (Panigrahi et al. 2005).

It was shown that isolated polysaccharides and extract of biological material containing polysaccharides and other substances are suitable for biosynthesis of nanoparticles. Isolated polysaccharides such as starch or heparin serve as both a capping agent and a reducing agent (Raveendran et al. 2003; Huang and Yang 2004). However, also some additional substances, such as  $\beta$ -D-glucose, can serve as a reducing reagent and starch can serve as a capping agent (Raveendran et al. 2003; Vigneshwaran et al. 2006).

### 7.2.2.5 Proteins

Synthesis of nanoparticles is also connected with presence of amino acids and proteins in plants extracts. It was observed that proteins act as both reducing and stabilizing agents. The big advantage of such prepared nanoparticles is their biocompatibility (Tan et al. 2010). On the other hand, the disadvantage is the speed of reaction. The synthesis is relatively slow (hours, days) in comparison to the other



plant metabolites (terpenoids, phenolic acids, flavonoids, saccharides), which took only few minutes (Ashraf et al. 2016; Baláz et al. 2017a). AgNPs synthesized by  $\text{AgNO}_3$  using extract of *Malva parviflora* were stabilized in solution containing proteins produced by the biomass (Zayed et al. 2012). Nitrogen of the amide group and silver ion coordination confirm the fact that the  $\text{NH}_2$  group of proteins has the strong capacity to capture the metal. It indicates that the proteins from plant extracts could cover the nanoparticles by layer, which has ability to avoid agglomeration and thereby to stabilize the solutions containing nanoparticles (Zayed et al. 2012). Although amino acids and proteins have the ability to reduce precursors of nanoparticles, they are very rarely used. Usually, different agents are used as reducers and proteins or amino acids serve only as capping agents, for example in bio-mechanochemical synthesis (Baláz et al. 2017a), simulated sunlight radiation (Huang et al. 2016) and sonochemical route (Ghiyasiyan-Arani et al. 2018).

### 7.2.3 Synthesis Procedure

After the extraction the solid residue is filtered off, the filtrate is used for nanoparticles synthesis. From literature survey, it follows that myriad of different plant extracts has already been used for the green synthesis of AgNPs (Ahmed et al. 2016; Ismail et al. 2016). We have selected just few recent interesting examples in our chapter. However, the principle of all the studies is always the same (Fig. 7.2).

The mostly used source of Ag(I) ions is silver nitrate aqueous solution in various concentrations. For example, aqueous extracts of *Adiantum capillus-veneris L.* were used for AgNPs biosynthesis by 1, 2 and 3 mM silver nitrate solution at room temperature via mechanical stirring (Omidi et al. 2018). The change of colour from yellow to dark brown was indication of silver nanoparticles formation. According to transmission electron microscopy (TEM) analysis, they synthesized nanoparticles of 18.4 nm size. Strong antibacterial activity was evidenced against both Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli*) bacterial strains.

Green synthesis of AgNPs using a root extract of *Lepidium draba* weed was successfully implemented by Benakashani et al. (Benakashani et al. 2017). As source of Ag(I) ions, they used 0.01 M  $\text{AgNO}_3$  with various amounts of root extract (2, 2.5,



Fig. 7.2 Schematic representation of green synthesis of silver nanoparticles by plant extract

3, 3.5 mL). The evidence of nanoparticles generating was visually controlled by colour change from green to dark brown as is generally known. The tested antibacterial activity was determined as higher as Ag(I) ions.

Seeds used for silver NPs synthesis were used by Ping and his colleagues (Ping et al. 2018). As reducing and stabilizing agent, they used grape seed extract and 0.01 M AgNO<sub>3</sub> was reduced. The average size of prepared AgNPs was 54.8 nm when synthesized at room temperature. Antibacterial activities have not been detected yet.

The very interesting and improved green synthesis method by photoreduction was used by Viet and his working group using the *Buddleja globosa* leaf extracts (Van Viet et al. 2018). For Ag nanoparticles synthesis, they used low-power UV light in the presence of poly (vinyl pyrrolidone) (PVP) as the stabilizing agent. The procedure was optimized (ratio of ethanol/water/silver nitrate; pH value and time of reduction) to obtain spherical Ag nanoparticles with average size of  $16 \pm 2$  nm. The prepared Ag nanoparticles were tested against *E. coli* strains with approximately 100% elimination.

## 7.3 Characterization Techniques

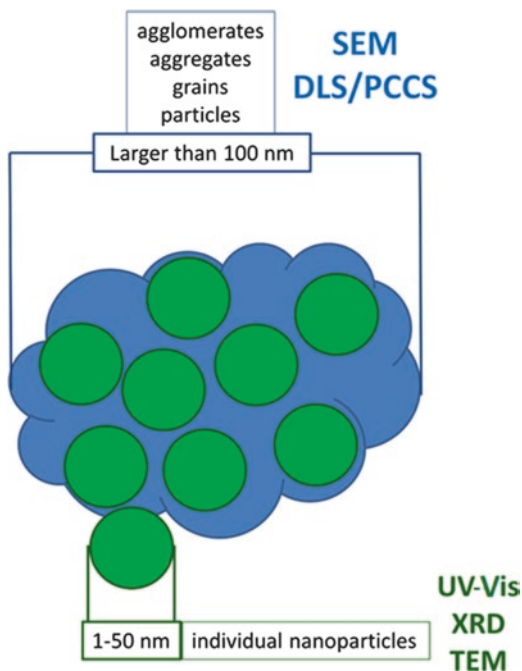
Characterization of Ag nanoparticles by various physical methods is very important in order to evaluate their physicochemical properties that can affect their behaviour, bio-distribution or safety. Synthesized silver nanoparticles are characterized by wide spectrum of methods including UV-Vis spectroscopy, infrared spectroscopy with Fourier transform (FTIR), X-ray photoelectron spectroscopy (XPS), dynamic light scattering (DLS), zeta potential, X-ray diffraction (XRD), scanning electron microscopy (SEM) and transmission electron microscopy (TEM). These techniques are very briefly reviewed below.

Very often, discrepancies in the papers regarding particle size determined by various methods occur. It is mainly because some methods focus on the individual nanoparticles, whereas the others on the large grains. This is explained by a very simplified figure (Fig. 7.3).

### 7.3.1 Ultraviolet and Visible Spectroscopy

Ultraviolet and visible spectroscopy (UV-Vis) is a broadly used method due to its availability, simplicity and sensitivity of measurement and is a relevant technique for the initial characterization of synthesized AgNPs by monitoring the synthesis during the process (Patil and Sastry 1997). In silver nanoparticles, the valence and conduction bands lie closely to each other, and electrons are able to move freely. This action leads to the formation of a surface plasmon resonance (SPR) absorption band occurring as a result of oscillation of AgNPs electrons with the wave of light

**Fig. 7.3** Schematic illustration showing which techniques report the size of individual nanoparticles of few nanometres and those that of agglomerates/grains of size larger than 100 nm

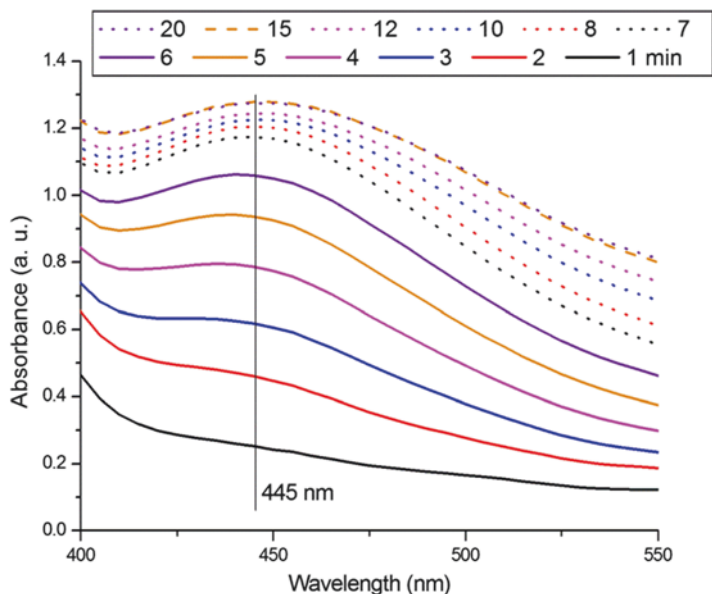


(Noginov et al. 2007; Van Der Merwe 2010). The absorption of Ag nanoparticle depends on the size of particles, dielectric medium and chemical environment (Noginov et al. 2007). The SPR band can serve as a simple detection of biosynthesized nanoparticles' stability with respect to unchanged wavelength of this absorption band (Zhang et al. 2016). As an example, the UV-Vis spectra showing surface plasmon resonance bands of AgNPs prepared by using the *Origanum vulgare L.* water extract (whole plant) and silver nitrate water solution (Baláz et al. 2017a) are shown in Fig. 7.4.

The time-dependent investigation of Vis spectra (Fig. 7.4) showed that soon after mixing *O. vulgare L.* water extract (showing two peaks in UV region) and silver nitrate water solution, the absorbance at 445 nm occurred, corresponding to the spherical silver nanoparticles. With reaction time, its intensity increased and after 7 min, the absorbance reached the maximum and after that, there were only slight changes (Baláz et al. 2017a).

### 7.3.2 Fourier Transform Infrared Spectroscopy

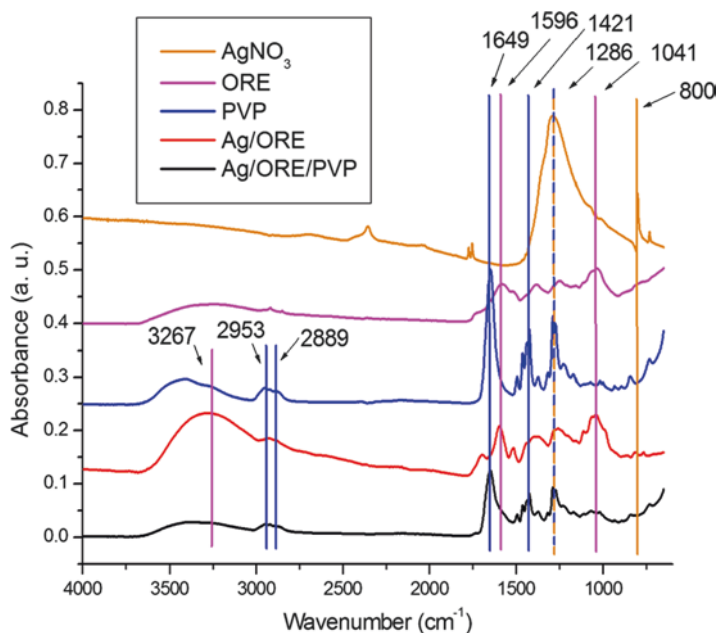
Fourier transform infrared spectroscopy (FTIR) represents accurate and reproducible possibility to detect small changes in functional groups by measuring absorbance. FTIR spectroscopy is relatively commonly technique used to identify which



**Fig. 7.4** Time-dependent absorption spectra during AgNPs synthesis and observation of SPR at 445 nm (Baláz et al. 2017a), copyright by Springer

molecules are responsible for bioreduction of Ag(I) ions in synthesis of AgNPs. In infrared spectra, the interactions between nanomaterials and biomolecules or the conformational states of bounded biomolecules (e.g. proteins) can be observed (Jiang et al. 2005; Shang et al. 2007; Lin et al. 2014). In addition to classical potassium bromide-based method, attenuated total reflection (ATR)-FTIR spectroscopy can also serve as a method for observation of the chemical changes on the surface (Lin et al. 2014). Sample preparation is much easier for conventional FTIR as there is no need to prepare pellet. ATR-FTIR method seems to be a good candidate for investigation of the surface characteristics of nanomaterial, but it is not a very sensitive technique at nanoscale due to its penetration depth and also because it has the same order of magnitude as the wavelength of IR (Liu and Webster 2007). As an example, ATR-FTIR spectra from the same study from where the UV-Vis spectrum, as shown, are provided (Fig. 7.5).

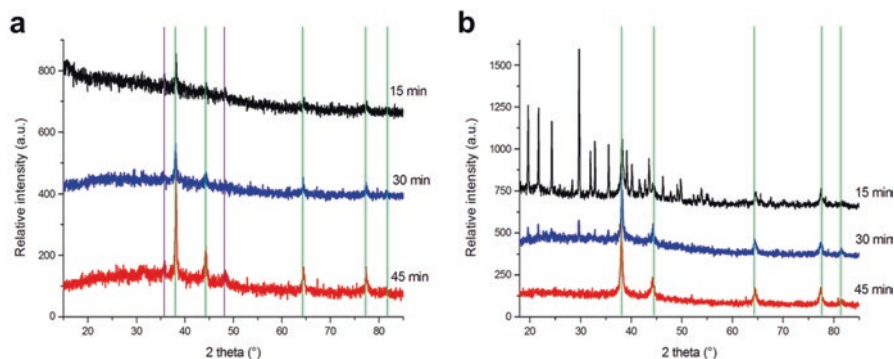
This complex, as shown in Fig. 7.5, provides a comparison of the FTIR spectra of all species included in the synthesis of AgNPs in the mentioned study. The spectra are described in detail in Fig. 7.5; however, the presence of  $-OH$  and the main peaks of the polymer in the spectrum of the final stabilized product can be emphasized. Also, no peaks of silver nitrate were observed in X-ray diffraction.



**Fig. 7.5** ATR-FTIR spectra of silver nitrate, pure *Origanum vulgare L.* extract (ORE), polyvinyl pyrrolidone and both PVP-stabilized and non-stabilized AgNPs (Baláz et al. 2017a), copyright by Springer

### 7.3.3 X-Ray Diffraction

X-ray diffraction (XRD) is very extended analytical method which can be used to analyse the structure of molecules as well as the crystal structures, qualitative identification of studied structures and, last but not least, the particle sizes (Singh et al. 2013). The X-ray light reflects on crystal, and this reflection leads to the formation of diffraction peaks that reflect structural characteristics of studied crystal. By XRD technique, a broad spectrum of materials from biomolecules, inorganic catalysts to polymers and nanoparticles and nanostructures can be analysed (Vaia and Liu 2002; Macaluso 2009; Khan et al. 2013). A rich plethora of compounds can be easily detected, as almost every phase has a unique diffraction pattern. There are, of course, exceptions, and then other techniques are necessary. It is also possible to identify impurities; however, the detection limit of commercial X-ray diffractometers is around 5%. This method has also some disadvantages including problems with crystal growth and the ability to obtain data related to single conformation (Sapsford et al. 2011). With regard to silver NPs preparation, it is very good method, as silver nitrate and silver are well-distinguishable. However, it is necessary to dry obtained powder for analysis. XRD patterns showing the progress of the bio-mechanochemical synthesis of AgNPs when using *Origanum vulgare L.* plant and eggshell membrane are shown in Fig. 7.6.

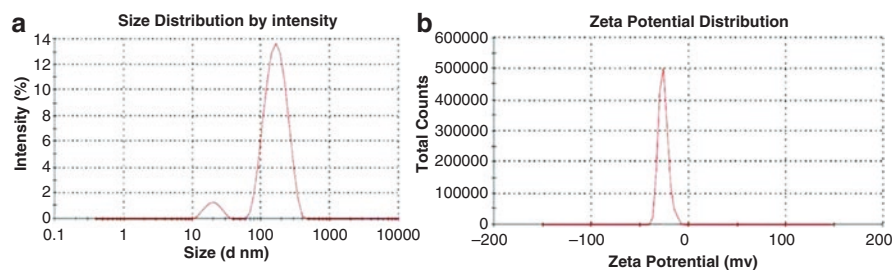


**Fig. 7.6** XRD patterns of AgNPs synthesized using  $\text{AgNO}_3$  and (a) ESM (eggshell membrane) mixture; (b) ORE (*Origanum vulgare*) mixture. Time of milling is included in figure, where green lines respond to the reflections of Ag (JCPDS 01–087-0717) and violet lines to WC (JCPDS 00–051-0939). All the non-marked peaks in (b) correspond to silver nitrate,  $\text{AgNO}_3$  (JCPDS 01–074-2076) (Baláz et al. 2017b), copyright by Elsevier

It can be seen that after 15 min, the peaks corresponding to elemental silver were already present in both studied samples. The synthesis was completed a little bit faster for the eggshell membrane and took only 30 min. In case of *Origanum vulgare*, L. after 30 min of milling, some peaks of  $\text{AgNO}_3$  were still visible, so the milling was conducted for 45 min in order to consume the remaining  $\text{AgNO}_3$ . In Fig. 7.6, also the reflections corresponding to qusonkite (WC, material of milling chamber and balls) can be seen after 45 min, which is a proof of the wear from milling media. Therefore, it was concluded that for Ag/ESM system, 30 min of milling is enough.

### 7.3.4 Dynamic Light Scattering

The dynamic light scattering (DLS) method is also commonly used for physico-chemical characterization of synthesized nanoparticles and plays an important role in size distribution of small particles in suspension or solution (Sapsford et al. 2011; Lin et al. 2014; Zhang et al. 2016). The mentioned method measures the scattered laser light passing through a studied sample and is based on interaction of light with the studied particles. DLS is a technique used for determining the scattered light intensity as a function of time, and the average hydrodynamic size of prepared nanoparticles dispersed in liquids can be determined (Sapsford et al. 2011; Zhang et al. 2016). An example of particle size distribution determined by DLS and results of zeta potential measurement (described below) for AgNPs prepared by green synthesis using *Origanum vulgare* L. is provided in Fig. 7.7. The particle size is bimodal, with the average value of 136 nm (Sankar et al. 2013).



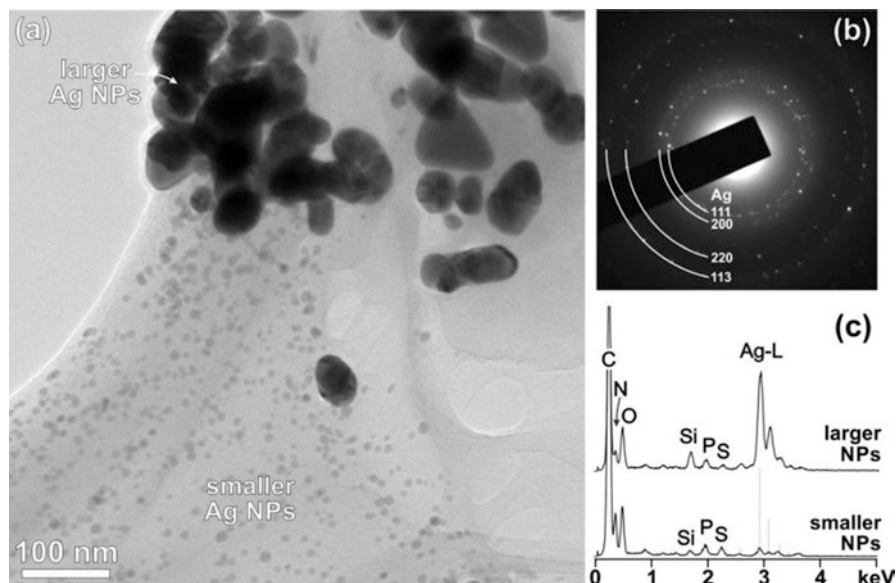
**Fig. 7.7** Particle size distribution determined by dynamic light scattering (a) and zeta potential measurement (b) of the silver NPs prepared by green synthesis (Baláz et al. 2017a), copyright by Springer

### 7.3.5 Zeta Potential

Zeta ( $\xi$ ) potential of nanomaterials in solution provides information about the charge of a nanoparticle-bioconjugate and its stability. Zeta potential is usually determined by application of an electric field across the prepared sample and measures the velocity at which charged species move to electrode (Pons et al. 2006). Zeta potential can also be applied to infer nanoparticles stability. Values with potential of 30 mV or more indicate stability, while values with potential lower than 30 mV predict particles with instability or agglomeration trend (Sapsford et al. 2011). However, this depends on the utilization of various stabilizers, as some of them act as steric ones, which do not affect the final zeta potential value then. The zeta potential measurement showing the detected value of  $-26$  mV is shown in Fig. 7.7b.

### 7.3.6 Transmission Electron Microscopy

Transmission electron microscopy (TEM) is a very important, valuable and frequently applied method for nanoparticles characterization. The electrons penetrate through the sample in this case. TEM technique is used to quantitatively measure particle size, morphology and size distribution. The TEM analysis provides good spatial resolution and possibility for other analytical measurements, but on the other hand, it requires high vacuum and thin sample section, so the preparation of the sample is very important in order to get high-quality and representative pictures (Lin et al. 2014; Zhang et al. 2016). For high magnification, high-resolution TEM (HRTEM) is used. Moreover, selected area diffraction (SAD) indicating the exact phase composition of the particular area in the samples can be recorded and subsequently compared with the XRD measurements. This analysis results in the rings or points in the reciprocal space, from which the interplanar distance can be calculated and individual crystallographic planes can be indexed. TEM is often connected with the energy-dispersive X-ray spectroscopy (EDX or EDS) providing information



**Fig. 7.8** (a) TEM images of the Ag/ORE/PVP indicating differentiation of the smaller and larger fractions of AgNPs. (b) SAD pattern of larger AgNPs fraction. (c) EDS spectrum of the larger and smaller AgNPs areas (Baláz et al. 2017a)

about individual elements present in the system. The example of TEM analysis of silver nanoparticles prepared by Baláz and his co-workers from water extract of *Origanum vulgare L.* after the stabilization with the polymer including SAD pattern and EDS spectra is provided in Fig. 7.8 (Baláz et al. 2017a).

Regarding particle size, two different populations can be detected from the samples, larger ones of about 38 nm and smaller ones of about 7 nm. The shape of the larger particles seems to be pseudo-octahedral, whereas the smaller ones exhibit spherical shape. These groups of nanoparticles are separated. The SAD patterns presented in Fig. 7.8b show the presence of silver with cubic crystal structure. The EDS spectra of the sample after stabilization (Fig. 7.8c) did not show only silver, but also other elements presented in the plant matrix.

### 7.3.7 Scanning Electron Microscopy

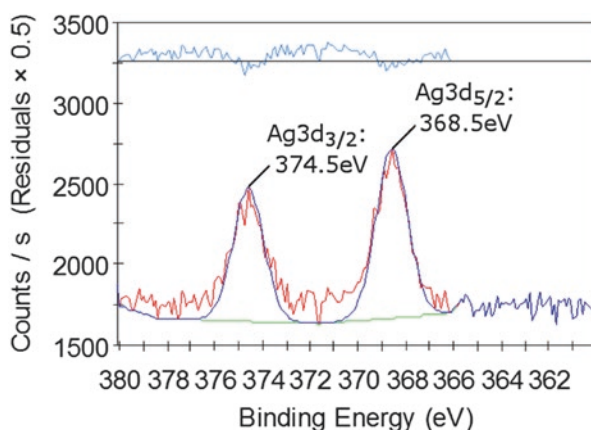
Scanning electron microscopy (SEM) method represents a valuable technique in surface imaging used in nanomaterials studies. In contrast with TEM, the electron beam ends on the sample. This method is appropriate for investigating particle size, size distribution and shape of nanoparticles and surface of prepared particles. By SEM technique, we can study the morphology of prepared nanoparticles and obtain



histogram from pictures by measuring and counting the particles manually or by software (Fissan et al. 2014; Lin et al. 2014; Zhang et al. 2016). The SEM method is also very often combined with EDX method; however, it is less accurate than in combination with TEM, as also bulk material (not seen on the photograph) is analysed (the beam goes deep into the material), Also, elemental mapping showing the distribution of individual elements is often used. The disadvantage of SEM is inability to resolve the internal structure of particles, as it is impossible to zoom so much to see individual NPs, but we can obtain valuable information about purity and aggregation of nanoparticles (Zhang et al. 2016).

### 7.3.8 X-Ray Photoelectron Spectroscopy

X-ray photoelectron microscopy (XPS) is an electron spectroscopy for chemical analysis (ESCA) and represents a valuable method to obtain qualitative and quantitative spectroscopic information of surface chemical analysis to obtain an estimated empirical formulae (Demathieu et al. 1999; Manna et al. 2001; Zhang et al. 2016). XPS technique is carried out under vacuum; X-ray irradiation of the nanoparticles leads to the emission of electrons, and the amount of escaped electrons from the surface of nanoparticles gives XPS spectra. The main advantage is that it can distinguish among different oxidation states of elements. An example of XPS spectra of bio-mechanochemically synthesized AgNPs showing only the peaks corresponding to elemental Ag(0) is shown in Fig. 7.9.



**Fig. 7.9** XPS spectra of AgNPs containing composite (Rak et al. 2016), copyright by Royal Society of Chemistry

## 7.4 Antibacterial Activity

Due to development of bacterial resistance of classical antibiotics, scientists are forced to find out more effective antibacterial compounds. There are many studies dealing with the synthesis and antibacterial and toxicological properties' testing of NPs. The silver NPs make no exception. The interest of the scientific community on silver nanoparticles as antibacterial agents has been increased in the last few decades. Unusual properties of AgNPs have led to their utilization in medicinal field, and the main attention is focused on their antimicrobial properties.

Many authors confirmed that Ag nanoparticles show antimicrobial effects and eliminate the bacteria even at low concentrations ( $\text{mg L}^{-1}$ ) (Panáček et al. 2006) without toxic influence on human cells (Carlson et al. 2008; AshaRani et al. 2009). As silver nanoparticles have shown potential as antibacterial substances, several methods are being used to evaluate their effect on different Gram-positive and Gram-negative bacterial strains. They will be briefly reviewed below.

### 7.4.1 Evaluation of Antibacterial Activity

Antibacterial activity studies are performed by different techniques, which lead to obtaining the results in different ways so the comparison of acquired data can be complicated. The mostly used methods of antibacterial activity evaluation are the determination of: (a) minimal inhibitory concentration (MIC), (b) half effective concentration ( $\text{EC}_{50}$ ), (c) minimal bactericidal concentration (MBC) and then (d) time-kill test, (e) disc-diffusion method and (f) well-diffusion method.

The commonly used method of evaluation of antibacterial activity is the disc-diffusion method. This well-known method is based on preparation of agar plates inoculated by tested microorganism. After incubation, the discs are impregnated with silver nanoparticles at desired concentration. Prepared agar plates are incubated under appropriate conditions for examined bacterial strains, and sensitivity analysis to AgNPs is carried out by measurement of the inhibition zone diameter around the disc or well. These methods are advantageous for simplicity and economic reasons and are commonly used for antibacterial activity of silver nanoparticles determination (Balouiri et al. 2016).

Antibacterial characteristics of AgNPs are most often studied by dilution methods and quantitative assays for the determination of MIC. MIC values represent the lowest concentrations of silver nanoparticles that completely inhibit the growth of tested microorganisms. The less common method for quantification of antibacterial activity in comparison with MIC method is MBC (minimum bactericidal concentration) and is defined as the lowest concentration of tested antibacterial compound that kills 99.9% of microorganisms after 24 h of incubation. The most suitable technique for the antibacterial effect is its determination by the time-kill test (or time-kill curve) and can also be applied for establishing the synergistic effect for

combination of two or more antimicrobial substances. These experiments offer the data about the dynamic interactions between various bacterial strains and tested antibacterial compounds. The time-kill test provides a time-dependent (usually 0, 4, 6, 8, 10, 12 and 24 h) or concentration-dependent antibacterial activity, and obtained data are typically presented in the form of graph (Balouiri et al. 2016).  $EC_{50}$  (effective concentration) and  $IC_{50}$  (inhibitory concentration) are used in discovery processes to determine suitability of the drugs. The  $EC_{50}$  is half maximal effective concentration referring of drug, which induces half-maximal response. The  $IC_{50}$  is the half maximal inhibitory concentration corresponding to the 50% control (Sebaugh 2011; Mohammadlou et al. 2016).

### 7.4.2 Antibacterial Potential of AgNPs

Silver in Ag(0) oxidation state is well-known as antibacterial agent and has been applied as therapeutics of some diseases since ancient time (Russell and Hugo 1994). Silver nanoparticles prepared by different ways were broadly examined on a large number of pathogens including Gram-positive and Gram-negative bacteria. Some works have shown that the silver nanoparticles are more effective against Gram-negative bacteria (Chopade et al. 2013; Kokila et al. 2016), but on the other hand, the opposite results have also been reported (El Kassas and Attia 2014). These differences in sensitivity can be explained by the differentiation in the thickness and composition of biomolecules presented in the biomembranes as the cell wall of Gram-positive bacteria is composed by peptidoglycans and is thicker than Gram-negative bacteria cell wall (Franci et al. 2015; Dakal et al. 2016; de Jesús Ruíz-Baltazar et al. 2018). The importance of antibacterial activity determination in various bacterial species becomes the essence of the need to understand the mechanism, resistance and future applications of Ag nanoparticles. Ultimate reports on antimicrobial activity are summarized in Table 7.1.

Though the antibacterial activity of AgNPs has been widely considered and reported, some factors affecting the AgNPs antimicrobial properties are arising, e.g. shape, size and concentration of NPs and capping agents (Ahmed et al. 2016; Aziz et al. 2015, 2016). Nakkala et al. (2017) studied Ag nanoparticles with average size of 21 nm and the size distribution was observed to be 1–69 nm when synthesized using medicinal plant *Ficus religiosa*. These synthesized silver NPs resulted in strong antibacterial effect against *Pseudomonas fluorescens*, *Salmonella typhi*, *Escherichia coli* and *Bacillus subtilis*. Lower concentrations of silver nanoparticles indicated delayed effect on bacterial cell growth which may be caused by the bacteriostatic effect, while at the concentrations of 60 and 100  $\mu\text{g}$ , the Ag nanoparticles showed bactericidal effect and no cell growth was detected. The green synthesized silver nanoparticles using the *Cynara cardunculus* leaf extract exhibited an antibacterial effect on *E. coli* and *S. aureus* at concentration of 20 mM; at lower concentration, the effect is minimal (de Jesús Ruíz-Baltazar et al. 2018). Antibacterial effect of AgNPs prepared by aqueous extracts from *Berberis vulgaris* using disc-diffusion

**Table 7.1** Selected methods used in antibacterial evaluation of green synthesized Ag nanoparticles

Method	Tested bacteria	Plant	Precursor	References
Agar well-diffusion method	G–: <i>E. coli</i> , <i>P. aeruginosa</i> , <i>K. pneumoniae</i> , <i>Salmonella typhimurium</i> , <i>Shigella flexneri</i> , <i>Proteus mirabilis</i>	<i>Fritillaria</i> (flower)	10 mM AgNO <sub>3</sub>	Hemmati et al. (2019)
	G+: <i>S. epidermidis</i> , <i>S. aureus</i> , <i>S. saprophyticus</i> , <i>S. pneumoniae</i> , <i>Streptococcus pyogenes</i> , <i>B. subtilis</i> , <i>Enterococcus faecalis</i> , <i>Listeria monocytogenes</i>			
MIC	G–: <i>E. coli</i>	<i>Berberis vulgaris</i> (root, leaf)	0.5, 1, 3, and 10 mM AgNO <sub>3</sub>	Behravan et al. (2019)
	G+: <i>S. aureus</i>			
MIC	G–: <i>E. coli</i> , <i>P. aeruginosa</i>	<i>Annona reticulata</i> (leaf)	1 mM AgNO <sub>3</sub>	Parthiban et al. (2018)
	G+: <i>S. aureus</i> , <i>B. cereus</i>			
Disc-diffusion	G–: <i>Enterobacter aerogenes</i> , <i>Pasteurella multocida</i>	<i>Coriandrum sativum L.</i> (leaf)	1 mM AgNO <sub>3</sub>	Ashraf et al. (2018)
	G+: <i>S. aureus</i> , <i>B. subtilis</i>			
Agar well-diffusion method	G–: <i>E. coli</i> , <i>K. pneumoniae</i>	<i>Cleome viscosa L.</i> (fruit)	1 mM AgNO <sub>3</sub>	Lakshmanan et al. (2018)
	G+: <i>S. aureus</i> , <i>B. subtilis</i>			
Disc-diffusion method	G–: <i>E. coli</i>	<i>Cynara cardunculus</i> (leaf)	50 mM AgNO <sub>3</sub>	de Jesús Ruíz-Baltazar et al. (2018)
	G+: <i>S. aureus</i>			
Agar-well diffusion method	G–: <i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. typhimurium</i>	<i>Origanum vulgare L.</i> (whole plant)	1, 2.5, 5, and 10 mM AgNO <sub>3</sub>	Baláz et al. (2017a)
	G+: <i>S. aureus</i> , <i>B. cereus</i> , <i>Listeria monocytogenes</i>			
Microdilution method, MIC	G–: <i>E. coli</i> , <i>P. aeruginosa</i>	<i>Pelargonium endlicherianum</i> (root)	5 mM AgNO <sub>3</sub>	Şeker Karatoprak et al. (2017)
	G+: <i>S. epidermidis</i>			
Agar well-diffusion method	G–: <i>E. coli</i> , <i>P. aeruginosa</i>	<i>Lantana camara</i> (leaf)	1 mM AgNO <sub>3</sub>	Shriniwas and Subhash (2017)
	G+: <i>S. aureus</i>			

(continued)

**Table 7.1** (continued)

Method	Tested bacteria	Plant	Precursor	References
Macrodilution broth method, MIC	G-: <i>E. coli</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i> , <i>P. vulgaris</i>	<i>Diospyros sylvatica</i> (root)	10 mM silver acetate	Pethakamsetty et al. (2017)
	G+: <i>B. subtilis</i> , <i>B. pumilis</i> , <i>S. pyogenes</i> , <i>S. aureus</i>			
Disc diffusion method	G-: <i>E. coli</i> , <i>K. pneumoniae</i>	<i>Carica papaya</i> (peel)	0.25–1.25 mM AgNO <sub>3</sub>	Kokila et al. (2016)
	G+: <i>S. aureus</i> , <i>B. subtilis</i>			
Agar well-diffusion method	G-: <i>E. coli</i> , <i>Pseudomonas</i> sp., <i>Klebsiella</i> sp.	<i>Alstonia scholar</i> (leaf)	1 mM AgNO <sub>3</sub>	Ethiraj et al. (2016)
	G+: <i>Bacillus</i> sp., <i>Staphylococcus</i> sp.			
Agar well-diffusion method	G-: <i>E. coli</i> , <i>P. aeruginosa</i> , <i>K. pneumoniae</i>	<i>Ocimum tenuiflorum</i> , <i>Solanum trilobatum</i> , <i>Syzygium cumini</i> , <i>Centella asiatica</i> , <i>Citrus sinensis</i> (leaf, peel)	1 mM AgNO <sub>3</sub>	Logeswari et al. (2015)
	G+: <i>S. aureus</i>			
Disc diffusion method	G-: <i>E. coli</i> , <i>P. fluorescens</i> , <i>S. typhi</i>	<i>Ficus religiosa</i> (leaf)	1 mM AgNO <sub>3</sub>	Nakkala et al. (2017)
	G+: <i>B. subtilis</i>			
Agar diffusion method	G-: <i>P. aeruginosa</i> , <i>S. typhi</i> , <i>E. coli</i> , <i>K. pneumoniae</i>	<i>Tamarindus indica</i> (fruit)	5 mM AgNO <sub>3</sub>	Jayaprakash et al. (2017)
	G+: <i>B. cereus</i> , <i>S. aureus</i> , <i>Micrococcus luteus</i> , <i>B. subtilis</i>			

MIC minimum inhibitory concentration, G- represents Gram-negative bacteria, G+ represents Gram-positive bacteria

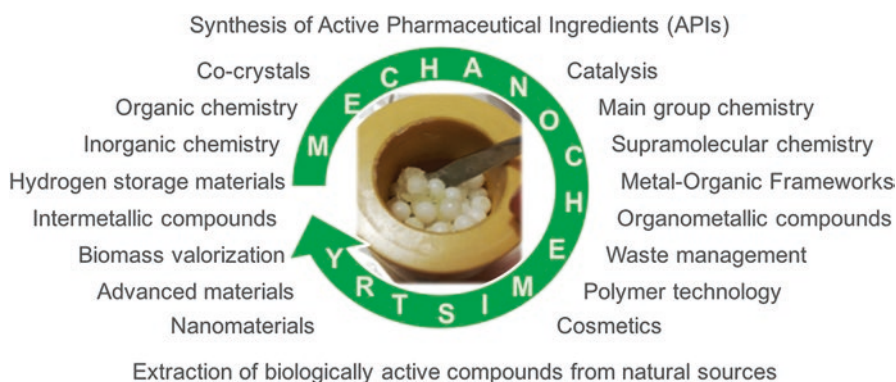
method at (1, 3, 5 mM) concentrations were evaluated on *S. aureus* and *E. coli*. As a negative control, water was used and as a positive control were chosen gentamicin and streptomycin. The MIC tests showed much higher antibacterial effect against Gram-negative bacteria, *E. coli*, than against Gram-positive, *S. aureus* (Behravan et al. 2019). Authors predict that silver nanoparticles have high affinity to sulphur and phosphorus-containing biomolecules, which is the main reason of AgNPs antibacterial properties. It means that silver nanoparticles influence the proteins containing sulphur which are concentrated inside and outside of the cell biomembrane and impact the possibilities of bacteria cell apoptosis (Yamanaka et al. 2005; Tamboli and Lee 2013). Antibacterial activity of silver nanoparticles is also affected by size and shape. It has been found that the smaller nanoparticles with larger surface-to-volume ratio exhibit higher antimicrobial effect than larger particles (Gurunathan 2015; Ethiraj et al. 2016; Deng et al. 2016). In general, higher

concentration of antimicrobial agent results in more effective antimicrobial effect, but particles with small size can lead to apoptosis of bacterial cells at a lower concentration. As we mentioned before, the shape of nanoparticles also influences the interaction with Gram-negative bacteria, for example *E. coli* (Ge et al. 2014; Deng et al. 2016). The interaction between AgNPs with different shapes and *E. coli* has been studied (Pal et al. 2007). The interactions were similar, but inhibition results were different. Authors discussed that AgNPs with the same surface area, but different shapes, may have unequal effective surface area in considerations of active facets. At that time, authors were unable to give an estimation of how the surface area of different NPs influences their ability to kill bacteria (Pal et al. 2007).

Many authors and reviewers have reported the mechanism of action of AgNPs in detail, but the strict mechanism of the antibacterial effect of silver and silver nanoparticles is not fully elucidated. Most of studies consider multiple mechanisms of action, but the main three different mechanisms are expected: (a) irreversible damage of bacterial cell membrane through direct contact; (b) generation of reactive oxygen species (ROS); and (c) interaction with DNA and proteins (Sintubin et al. 2012; Durán et al. 2016; Sheng and Liu 2017; Rajeshkumar and Bharath 2017; Aziz et al. 2015, 2016, 2019) (Fig. 7.10).

## 7.5 Bio-mechanochemical Synthesis

Mechanochemistry has been in existence for a very long time, but its name was established much later. For example, creating fire by just banging two stones together in ancient times can be also considered mechanochemistry. Valuable works regarding history of this branch of chemistry were written by Takacs (Takacs 2004, 2013, 2018). Among many others, at least two important mechanochemists from the past can be mentioned, namely Carey Lea and Ostwald. The first one found out that the application of energy in the form of pressure and temperature yields different

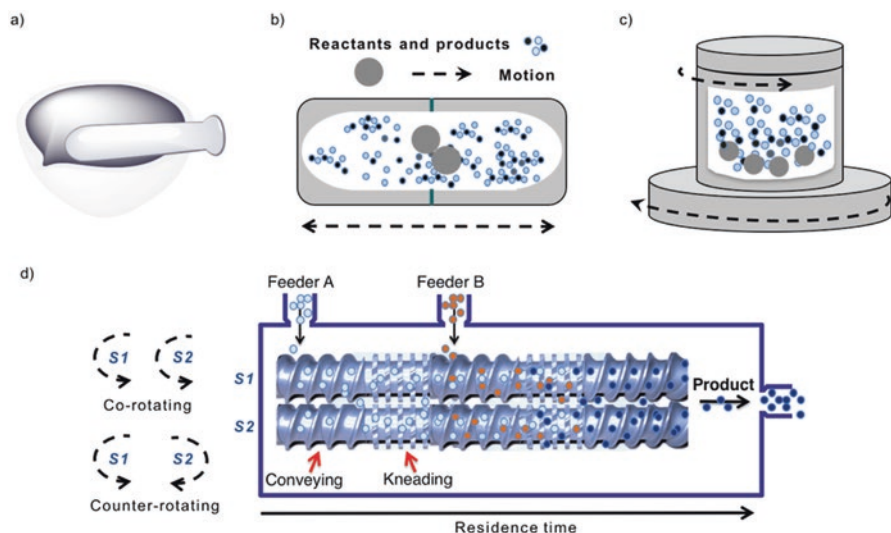


**Fig. 7.10** Fields of applications of mechanochemistry (Baláž et al. 2019)

results (Lea 1893). Particularly, if temperature is applied on mercury or silver chloride, just sublimation occurs, whereas pressure effect results in the decomposition of these compounds into elements. Ostwald put the term “mechanochemistry” on the same level as thermochemistry, photochemistry and electrochemistry (Ostwald 1919). Since these preliminary works, mechanochemistry underwent a great development. Recently, it has penetrated into almost every branch of chemistry and materials science, for example pharmacy, organic synthesis, waste management, extraction of biologically active compounds from natural resources, nanotechnology, catalysis, etc. (Boldyreva 2013).

The term “mechanochemistry” is composed of two words: mechanics and chemistry. In simple words, by supplying the mechanical energy, it is possible to perform chemical reactions which would normally need higher temperatures or organic solvents under ambient conditions directly in solid state, which brings about very important environmental aspect. From the physical point of view, the energy is supplied to the powders by milling. The materials can be treated for two reasons, either to activate material or to perform reactions. The milling process can be conducted in dry or wet environment. There are many types of mills applying many different regimes (like pressing, shearing, impact, etc.). The principles of work of some basic high-energy mills are described in Fig. 7.11 (Baláz et al. 2019).

Most mechanochemical experiments are performed on a laboratory scale; however, the scale-up of this method is also gaining importance, namely, its wide usage in pharmaceutical industry (Al Shaal et al. 2010).



**Fig. 7.11** Working principles of selected mechanochemical devices: (a) mortar and pestle, (b) shaker/vibratory mill (horizontal and vertical oscillations are possible), (c) planetary ball mill, (d) continuous twin-screw extruder. Adapted from ref. (Baláz et al. 2019)

The mechanochemical approach is also very important for nanomaterials synthesis (Baláž et al. 2013). Particularly, it represents a top-down approach by creating nanoparticles by comminution of coarse materials. The other strategy is to use the micro-sized elements for the preparation of the compounds with crystallite sizes in nano-range. This can be achieved by high-energy milling. Another possibility is the utilization of ultrafine milling (e.g. wet stirred media milling) (Romeis et al. 2016), where the size of the product is diminished into very small particles, which can be applied, for example, in biomedicine as nanosuspensions (Peltonen and Hirvonen 2010).

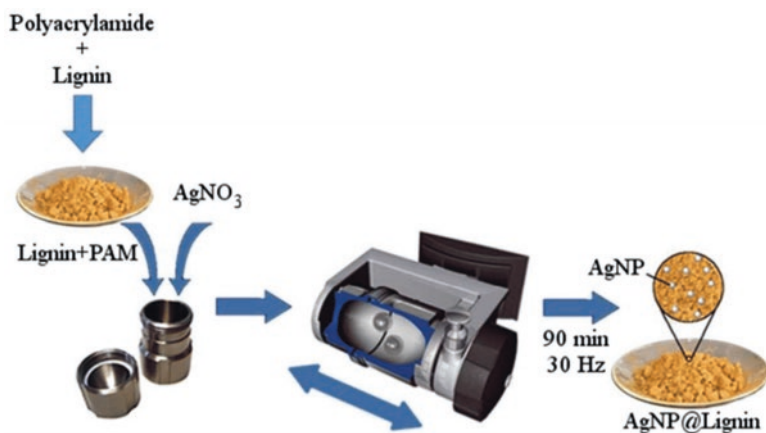
At the very beginning of the new millennium, nanoparticles synthesis by this method was just starting and a short review paper by McCormick and Tsuzuki was elaborated (Tsuzuki and McCormick 2004). Different metallic nanoparticles were successfully prepared by reduction of corresponding chloride with sodium metal. The authors also introduced a concept of dilution agent (NaCl in this case), because the reactions were exothermic, and it was necessary to avoid combustion. Also, the use of smaller grinding balls was beneficial as it also delayed the combustion. Many binary oxides and sulphides with particle size in the nanorange were successfully synthesized by the same research group from the corresponding chlorides. Since that time, the field broadened significantly, as pointed out earlier (Baláž et al. 2013).

There is a large number of papers on silver nanoparticles synthesis using mechanochemistry. One of the approaches is the utilization of AgCl as silver precursor, and the reduction is achieved via displacement reaction with another metal (Keskinen et al. 2001; Le et al. 2008; Khakan et al. 2017). In other works, composites of AgNPs with different compounds for various applications were prepared (Wang et al. 2010; Dai et al. 2016; Chambers et al. 2017). A cryomilling of micro-sized elemental Ag was also used (Kumar et al. 2016). The mechanochemical reduction of Ag<sub>2</sub>O (Khayati and Janghorban 2012) or AgNO<sub>3</sub> was also used (Tiimob et al. 2017).

However, the reports utilizing natural materials for mechanochemical synthesis of AgNPs are very scarce. Namely, the utilization of materials of plant origin is an unexplored field. Such an approach can be called bio-mechanochemical synthesis and in further text, few works in which the combination of mechanochemistry and plant material for the production of AgNPs has been applied are discussed.

The first paper elaborated by Rak et al. in 2016 reports on the preparation of silver nanoparticles by ball milling method, in which lignin serves as a reducing agent and polyacrylamide (PAM) as a supporting polymer (Rak et al. 2016). During the synthesis, AgNO<sub>3</sub> was used as a source of silver. Regarding reducing agents, two types of lignin were used, namely commercially available one (Kraft lignin—KLig) and synthetic one (Thermomechanical pulp lignin—TMPLig). In the second case, lignin was prepared from TMP by oxidation prior to experiments. The difference between the two lignins is in the fibre size, as TMP lignin is larger and its structure is very similar to original lignin, so it can be also called natural lignin. At first only solid AgNO<sub>3</sub> and lignin were milled for 90 min and AgNPs were obtained. However, as the authors wanted to use the product in the antibacterial filters, an introduction of the third component, namely polyacrylamide (PAM), was necessary.





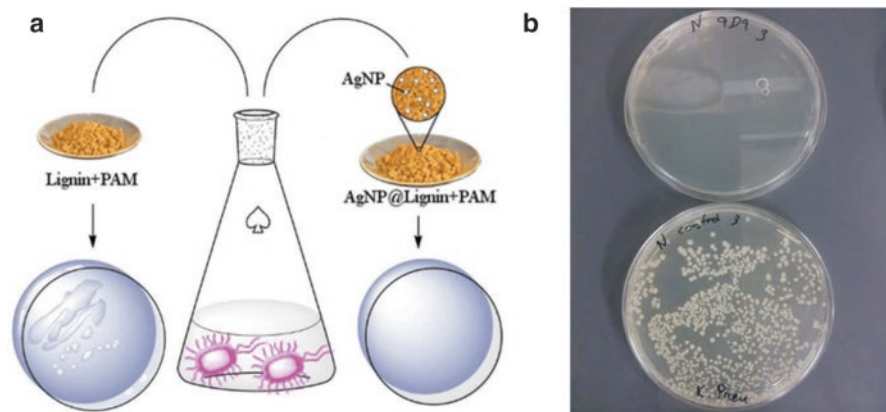
**Fig. 7.12** Scheme of mechanochemical synthesis of AgNPs/lignin/polyacrylamide composites (Rak et al. 2016)

At first, lignin was left to form a composite with PAM, and then it was co-milled with AgNO<sub>3</sub> under similar conditions as in the case of PAM-free experiments. In Fig. 7.12, the scheme of the whole synthetic process is demonstrated.

Using TEM, the authors have shown that the prepared AgNPs were embedded in the organic lignin matrix. In the samples with PAM, AgNPs are encased in the polymer. The AgNPs were spherical and polydisperse with same range of sizes in all prepared samples so the PAM or the used type of lignin did not affect studied AgNPs in matter of size and shape.

The results of PXRD confirmed the presence of elemental silver. The authors also used XPS method (the spectrum was already shown in Fig. 7.9) and observed a peak located at 368.5 eV, which supports the presence of Ag in the zero-valence form. FTIR spectra have shown the peaks corresponding to lignin and PAM also in the AgNP-containing samples, thus showing that the structure of the materials was maintained.

The antibacterial activity was tested on two Gram-positive (*S. aureus*, *Enterococcus faecium*) and three Gram-negative (*Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *E. coli*) bacteria. For antimicrobial tests, the Kraft lignin was selected and two types of porous plugs were prepared. One consisted of AgNPs, Kraft lignin and PAM while another only Kraft lignin and PAM without any silver in it. Afterwards, the bacterial dispersion was passed through the plugs, and filtrates were diluted and inoculated onto agar plates. On the agar plates incubated with solutions that were passed through the silver-containing composites, no bacterial growth was noticed. On the contrary, no inhibition of bacterial growth was observed on the agar plates that were treated with the AgNPs-free solution. The scheme of this process and the photographs of the agar plates are presented in Fig. 7.13a and b, respectively.



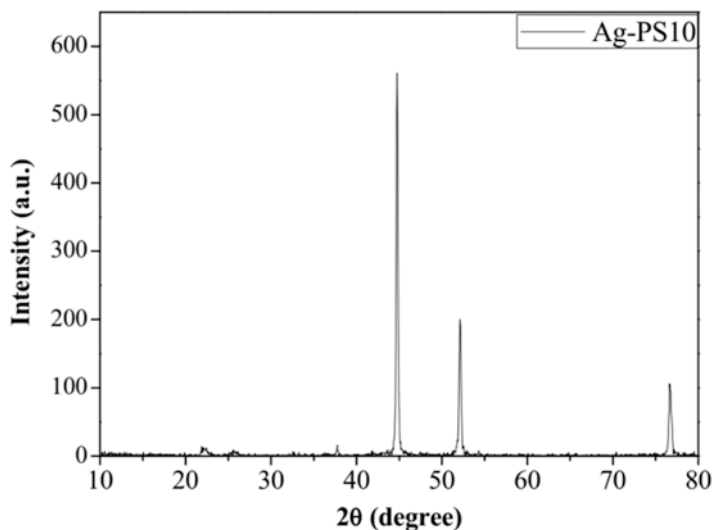
**Fig. 7.13** (a) Schematic illustration showing the antibacterial activity of AgNP@Klig/PAM; (b) photos of agar plates incubated with a solution of *K. pneumonia* that were passed through the filter plug with a silver-containing composite AgNP@Klig/PAM (top), and the silver-free Klig/PAM control (bottom). Reprinted from (Rak et al. 2016) [17], copyright by Royal Society of Chemistry

The authors showed that mechanochemically prepared AgNPs@Klig/PAM possesses antibacterial activity and generated adequate amounts of Ag(I) to be able to eliminate all studied bacterial strains. The mechanism of antibacterial activity of silver nanoparticles most probably lies in the local oxidative generation of Ag(I) ions at aerobic conditions, which releases antimicrobially active silver ions in contact with water (Xiu et al. 2012).

The utilization of biomass-derived polysaccharides as a reducing agent for AgNPs synthesis was realized by Arancon et al. in 2017 (Arancon et al. 2017), namely, the polysaccharides were isolated from the fungi *Abortiporus biennis* (PS1), *Lentinus tigrinus* (PS2), *Rigidoporus microporus* (PS5) and *Ginkgo polypore* (PS10). The polysaccharides were then ball-milled with AgNO<sub>3</sub> in the ratio 1:2 for 30 min. After milling, the obtained powders were calcined at 600 °C to remove the unbound organic matrix. Finally, the toxicity of the products was investigated by MTT assay.

The first part of the paper is devoted to the characterization of the prepared AgNPs. The authors also focus on the interaction between polysaccharides and AgNPs by using FTIR, and they registered some bands corresponding to organics species, as some functional groups could still be detected in the spectra, despite the calcination step. This points to successful interaction. The calcined Ag-PS10 powders were further investigated by X-ray diffraction (Fig. 7.14).

A non-traditional result pointing to the preparation of silver in hexagonal crystal structures was observed. The authors claim that they have also cubic silver, but the intensity of the main peak, which should be located at 2 theta value at 38.1°, is really low, and the same situation is also with the third most intensive peak of cubic phase which should be located at 64.5°. The authors claim that they have the combination of both crystal structures based on the TEM analysis; however, the actual crystal



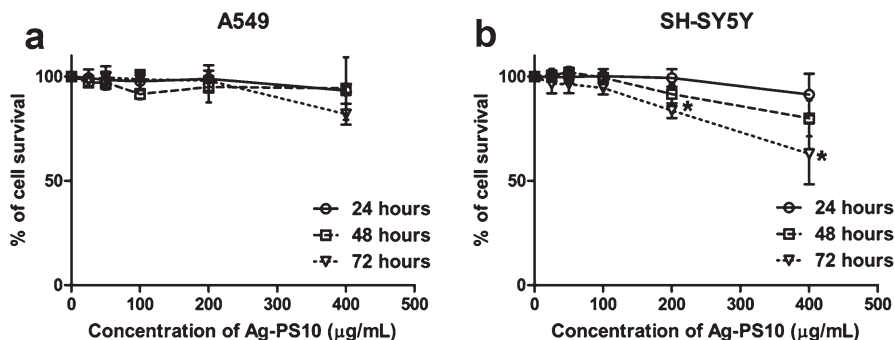
**Fig. 7.14** XRD pattern of Ag-PS10 sample (Arancon et al. 2017), copyright by Elsevier

structure does not have to be the same as the actual shape of the particles. Namely, in most papers, spherical AgNPs are observed (mostly claimed based on UV-Vis measurements), but when XRD is done, the authors observe cubic reflections (Sankar et al. 2013). The authors have also used XPS method with the conclusion that they have Ag in elemental form, as the position of Ag peak was at 368.1 eV and it fits in the range between 368.0 and 368.3, which, according to the authors, corresponds to Ag in this oxidation state. Also, the thermal decomposition during calcination showing the evaporation of residual moisture and decomposition of unbound organics was observed.

The second part of paper is devoted to the MTT assay to show the toxicity on two human cell lines, namely A549 lung adenocarcinoma and SH-SY5Y neuroblastoma cell line. The products have shown almost no toxicity towards the studied cell lines; a statistically significant decrease in viability was observed only in one case when the highest concentration was used. The example is presented for Ag-PS10 sample (Fig. 7.15).

In the end, the authors also analysed the Ag content in the soluble silver supernatant of Ag-PS nanohybrid dispersions in supplemented cell culture media, and they detected higher amount of Ag in the media of A549 cell line.

The mechanochemical approach was also applied as a stabilization procedure after the classical green synthesis (Baláž et al. 2017a). Firstly, Ag nanoparticles have been prepared by a classical green synthesis in liquid medium by mixing silver nitrate water solution and aqueous extract of *Origanum vulgare*, L. (whole plant was used). Generation of AgNPs was monitored by measuring the UV-Vis spectra (Fig. 7.4) and also by visual colour change of the solution from light brownish



**Fig. 7.15** The percentage cell viability estimated by MTT test on (a) A549 and (b) SH-SY5Y cell lines using increasing concentration of Ag-PS10 NPs (0, 25, 50, 100, 200 and 400  $\mu\text{g mL}^{-1}$ ) after exposition time of 24, 48 and 72 h. An OD value of control cells (unexposed cells) was taken as 100% viability (0% cytotoxicity). Results were displayed as mean  $\pm$  SD of three independent experiments (\*significantly different from control;  $p < 0.05$ ). Reprinted from (Arancon et al. 2017), copyright by Elsevier

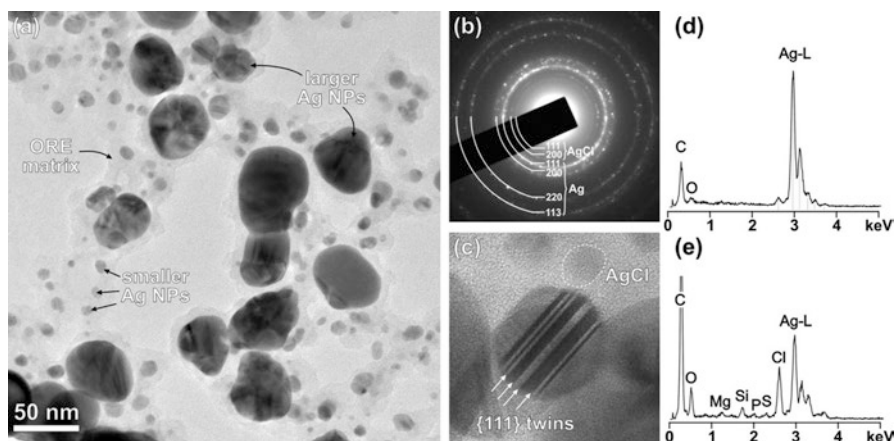
yellow at the beginning to dark brownish red at the end of the reaction. The reaction was completed after 15 min and subsequently, the stabilizing agent, polyvinylpyrrolidone (PVP) was added to the prepared nanosuspension. The effect of milling on the particle size distribution was studied. The authors found out that before the milling with PVP, two fractions of particles were present with sizes ranging between 110 and 330 nm for the larger one and between 15 and 80 nm for the smaller one. After the milling for 60 min, bimodal particle size distribution was also observed, but the milling decreased the average size of nanoparticles.

The increase in the intensity of the SPR peak with reaction time was already described earlier (Fig. 7.4). After the stabilization with PVP, this peak was red-shifted to 472 nm.

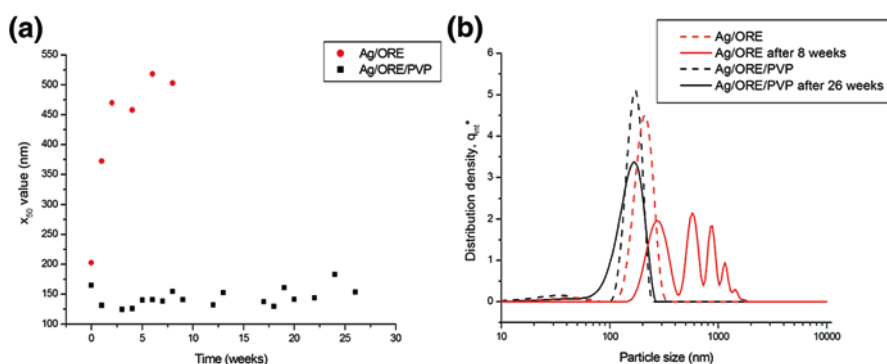
The final sample after green synthesis and the PVP-capped NPs were investigated in terms of photoluminescent properties. In the case of PVP-free AgNPs, just two weak emission peaks were recorded. On the other hand, sample of AgNPs with PVP exhibited one strong emission peak, which indicated that the addition of PVP enhances the photoluminescence emission intensity. Also, infrared spectroscopy (FTIR) was employed for the characterization (Fig. 7.5).

The transmission electron microscopy (TEM) was used to analyse the size, morphology and distribution of AgNPs both in the absence and presence of PVP. The results for the PVP-stabilized sample are shown in Fig. 7.8. The TEM analysis of the sample prior to stabilization is shown in Fig. 7.16.

As already mentioned, two different populations were found in both samples. In the sample without PVP, the populations were intermixed and dispersed in *O. vulgare* matrix, whereas after the stabilization, the separation of these groups occurred. The SAD pattern presented in Fig. 7.16b shows mainly the presence of silver with cubic crystal structure, but also the presence of AgCl was detected. Such particle is shown in Fig. 7.16c. Also, twinning phenomenon, common for silver NPs, was



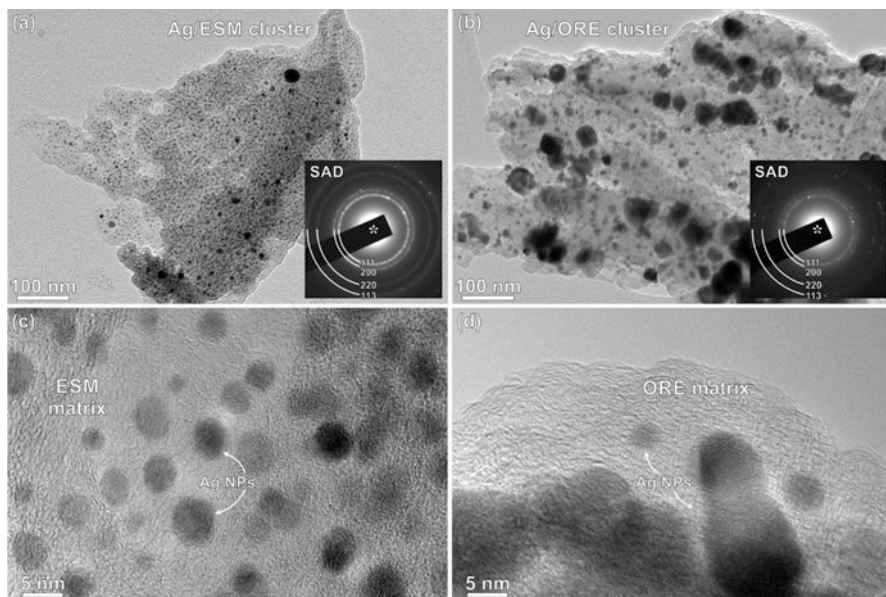
**Fig. 7.16** Transmission electron microscopy (TEM) images of Ag/ORE sample. (a) Particle size distribution at low magnification (b) SAD pattern (c) larger AgNPs is the presence of parallel twins; a small particle of AgCl displaying weaker contrast due to the lower average density is encircled (d) EDS spectrum of larger AgNP and (e) EDS spectrum of small AgNPs in ORE matrix (Baláz et al. 2017a), copyright by Springer



**Fig. 7.17** Stability of the Ag/ORE/PVP and Ag/ORE nanosuspensions. (a) The hydrodynamic particle diameter, ( $x_{50}$ ) change with the time of storage. (b) Particle size distribution (Baláz et al. 2017a), copyright by Springer

observed as it is shown in the same figure. From the EDS spectra in Fig. 7.16d and e, almost pure silver in the case of larger particle and considerable amount of chlorine in the case of smaller AgNPs with *Origanum* remains were detected.

The last part was devoted to the stability studies. Zeta potential and photon cross-correlation spectroscopy (PCCS) (quite similar to DLS method) were the techniques used for demonstrating the stability of prepared nanoparticles. After the addition of PVP, the zeta potential decreased, which is the proof of stabilization of the system. PCCS has shown the formation of agglomerates and a quick increase in average hydrodynamic particle diameter during storage of the PVP-free sample (this can be well seen for Ag/ORE sample after 8 weeks). As can be seen in Fig. 7.17, the



**Fig. 7.18** (a) TEM images of Ag/ESM and (b) Ag/ORE at low magnification with inserted SAD patterns indicating the crystallinity of AgNPs in both samples. (c) HRTEM image of well-dispersed AgNPs in ESM matrix and (d) agglomeration of AgNPs in the ORE matrix. (Baláz et al. 2017b), copyright by Elsevier

introduction of PVP into the system led to a noticeable enhancement in the stability of the nanosuspensions. The average hydrodynamic particle diameter did not increase significantly during 26 weeks storage at 4 °C.

The main added value of this paper is the introduction of wet stirred media milling for the stabilization of silver NPs. The antibacterial activity was not investigated in this study.

The last paper to be discussed in this sub-chapter is the completely solid-state approach (Baláz et al. 2017b). An eggshell membrane (ESM) and *O. vulgare*, L. (ORE) plant were used as natural reducing agents. As a silver precursor, silver nitrate was used. The whole synthesis was accomplished in planetary ball mill with the ratio of AgNO<sub>3</sub> to eggshell membrane or *O. vulgare*, L. plant 1:1. The course of reaction was followed by X-ray diffraction, as already described in Fig. 7.6.

From the SEM images, the AgNPs embedded within the organic matrices of both materials could be identified. In the case of Ag/ORE sample, the NPs seemed to be denser. Besides silver, the EDS analysis has shown the presence of phosphorous and chlorine coming from the matrix of Ag/ORE sample. Also, zeta potential in water was measured, yielding more negative value for Ag/ORE sample, which suggests its better stability.

TEM analysis of both samples confirmed the presence of AgNPs dispersed in the organic matrix (Fig. 7.18). The AgNPs differ in size, namely Ag/eggshell membrane sample is comprised of smaller particles than Ag/*O. vulgare* sample. In the latter

sample, the separate nanoparticles have tendency to merge and form larger clusters. Therefore, two different populations of nanoparticles are present in this sample. This phenomenon was not observed for Ag/eggshell membrane composite.

Both samples were also tested for antibacterial activity on six strains of bacteria (three Gram-positive and three Gram-negative) at four different concentrations (1, 2.5, 5 and 10 mM). The antibacterial activity is expressed as the percentage of relative inhibition zone diameter (RIZD) with respect to gentamicin standard antibiotic. In the case of pure biomaterials, no antibacterial activity was detected. In Ag-containing samples, the antibacterial activity was observed. The antibacterial activity was higher for the nanoparticles prepared with *Origanum vulgare*, *L.* plant. Also, the lowest concentration (1 mM) was not effective in inhibiting bacterial growth, whereas in the case of *L. monocytogenes* and *S. aureus*, small antibacterial activity of sample Ag/*O. vulgare* was observed. The Ag/*O. vulgare* nanoparticles at concentrations 2.5, 5 and 10 mM reduced the growth of all tested bacteria. The concentration 2.5 mM was quite interesting because in four of six studied bacteria, the antibacterial activity was higher than those with 5 mM concentration. It is possible that the silver ions had better distribution in *Origanum vulgare*, *L.* matrix and thus better effect. The antibacterial activity towards all studied bacteria for Ag/eggshell membrane sample was observed at 5 and 10 mM AgNO<sub>3</sub> concentration.

The last discussed study could ignite a new research field, which could be called bio-mechanochemical synthesis as it combines the tools of mechanochemistry and green synthesis (bio-approach) using plants. Together with the studies mentioned earlier, it definitely opens new possibilities and brings mechanochemical research closer to nature.

## 7.6 Conclusion

From the economical (low cost) and environmental point of view, the plant- and plant extract-based synthesis represents a green chemistry-based approach for silver nanoparticles synthesis and has opened new ways in treating and/or controlling various diseases of humans. This approach avoids the problem of using hazardous chemicals and subsequent addition of stabilization agents. Nature is the source of enormous number of extractable biomolecules (e.g. terpenoids, sugars, alkaloids, polyphenols, flavonoids, proteins) suitable for reduction of silver ions. Commonly used characterization techniques (UV-Vis, FTIR, XRD, SEM, TEM, etc.) can be also used to describe green-synthesized nanoparticles to evaluate and control the particle size, size distribution, shape of nanoparticles or to detect the degree of agglomeration. The last part was devoted to bio-mechanochemical synthesis of AgNPs, which represents a combination of mechanochemistry being a relatively old branch of chemistry, with biosynthesis using plants. This approach is still very rarely described in literature. The combination of mechanochemical-assisted extraction (MCAE) of plant materials and bio-reduction of silver ions in one-step procedure and could open a new research pathway.

Generally, nanoparticles with antimicrobial properties are qualified as a promising variant to antibiotics. They represent an appreciable future prospective in consideration in the development of pathogen-resistant solution. Ultimately, silver nanoparticles used in medical and pharmaceutical field are a rapidly developing field of science where the green synthesis provides easy and environmentally acceptable access to them.

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