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Article

The planetary ball milling of different powders yields similar granulometry

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Abstract: The main objectives of nanotechnology include the establishment of processes for the development and control of the nanoparticles' size and shape. Bottom-up or top-down methods can be used to achieve these objectives, but independently various parameters such as rotational speed, temperature, revolution time, and others must be controlled. However, both methods can be expensive, especially from an industrial point of view. To reduce production costs, we have investigated the feasibility of applying an identical top-down process to compounds with different chemical and physical properties. Starting from powders with very variable particle size, we arrive at powders with a particle size practically indistinguishable from the point of view of pharmaceutical technology. This procedure can be useful in industrial preparations.

Keywords: ball milling; DLS; nanoparticles; nutraceuticals; top-down method

1. Introduction

In clinical phase IV, pharmaceutical research tries to identify rare adverse reactions or harmful effects, assess efficacy, and optimize the drug's use. It supports label expansions or new indications that might come to light. Among others, the industrial research improves drug performance and patients' compliance. One strategy is the optimization of drug formulation, for example, to increase its bioavailability and biocompatibility and reduce its dosage [1]. Furthermore, these advantages allow for the extension of the patent life of a drug. An approach to improve the pharmacokinetics of a drug is to reduce its particle size. The particle size directly affects the solubility, bioavailability, and efficacy of the ingredients in the human body; the optimal size range affects drug absorption [2]. Drug delivery systems (DDSs) are considered an important target of pharmaceutical research, potentially enhancing drug efficacy and safety. The DDS strategy changes from small drugs to large biological molecules such as proteins, but regardless of molecular size, powder properties can affect the industrial production chain. To control the granulometry of the processing powders, which include both the active and non-active ingredients, is among the main technological objectives of pharmaceutical research [3,4]. In addition, reducing costs along the production chain is another objective of industrial research, especially when a drug is already on the market. Currently, among the various technologies that can meet pharmaceutical industry needs, nanotechnology provides the best approach to reduce the size of powders and promises some benefits for the patients and for the pharmaceutical industry, including reduced manufacturing costs [5]. The application of nanotechnology to compounds of pharmaceutical interest is fairly recent but it is based on studies that

have their roots in the most important discoveries of physics at the end of the 19th century [6].

It is known that the work of Paracelsus inspired Michael Faraday to prepare the first pure sample of colloidal gold in 1857, which he called «activated gold». Faraday used phosphorus to reduce a solution of gold chloride and was the first to understand that the color was due to the very small size of the gold particles [7]. Following this discovery, several studies were conducted to explain the behavior of nanomatter until, in 1959, Feynman, in a famous lecture, explained the importance of the nanometric dimension and illustrated possible scenarios of the nanodimensional space. On the other hand, since gold has high electrical conductivity and high chemical and thermal stability, gold nanoparticles have found numerous applications in superconductor physics and electronics. Over the last century, the applications of nanometric matter have increased in different industrial fields, including medicine [8]. Nanomatter is distinguished from colloidal matter because it has at least a size ranging from a few to 100 nanometers. All sizes of a colloidal material are between 100 nm and 1000 nm, and at higher sizes we find sub-millimetric matter. Due to the low density and size of nanoparticles versus sub-millimetric particles, their surface-to-volume ratio increases. Furthermore, independently from their electric charge, interaction with the solvent interface increases their solubility.

These properties can improve the performance of pharmacological compounds that are formulated from millimeter-sized powder. Among the various properties, nanoparticles are comparable in size to those of their drug targets and therefore have high bioavailability [9]. The first nanoparticles used as medicines were obtained by using gold atoms. The atomic radius of gold is 146 nm. Its molecule, at room temperature, has a face-centered cubic crystal structure with an interatomic distance of 0.407 nm, center to center, and an atomic packing factor of 0.74 and 26% is the remaining empty space. These characteristics make gold capable of forming clusters of atoms that, in the presence of ions, self-assemble into gold nanoparticles (GNs). GNs have found several applications in super-electronics and medicine [10]. They were used for dental prostheses or for the treatment of certain diseases, such as rheumatoid arthritis [11]. Many atoms or substances, such as silver or cerium oxide, under particular physical conditions, have the property of self-assembling into nanometric structures slightly larger than the molecule, showing completely unexpected characteristics [12,13]. Consequently, one of the first methods to obtain nanoparticles was to obtain atoms or molecules that could self-assemble into larger structures at the nanometric scale.

In recent years, the benefits of the nanoscale have also been exploited to synthesize organic nanoparticles, particularly for use in medicine [2]. With the evolution of technologies and the need to work also with other types of compounds, methods have been sought to obtain nanoparticles even starting from material with granulometry in the millimeter scale. In the medical field, in particular, there have been cases of lipophilic or toxic compounds or ones that are poorly absorbed, requiring the development of systems suitable to deliver these substances [14,15]. A solution has been provided by enveloping compounds in nanocarriers such as nanolipids, nanomicelles, or nanopolymers [16,17]. Generally, drug-containing nanoparticle systems have relatively low drug loads, thus generating problems of

either insufficient concentration to carry out the pharmacological action or too large an amount of preparation to be administered, such that it causes adverse side effects [18]. In addition, drug loading should not be confused with the encapsulation efficiency, which is defined by the ratio between the weight of the drug in the nanoparticles and the weight of the drug used in the preparation. Typically, this is the value that is reported, which can vary between 10% and 90%, depending on the method of nanoparticle preparation. In recent years, much research in the field of nutrition has been directed toward the development of new functional foods (nutraceuticals) that are more water soluble, sensory-appreciable, more thermally stable, and have good oral bioavailability [19]. Nutraceuticals are products that, in addition to their nutritional value, have the power to positively influence body physiology and, by this view, have a pharmacological behavior. Drug powders are available on the market as millimeter powders, and although there are several formulation strategies, only a small portion of the administered dose is absorbed due to their poor bioavailability. Therefore, effective vehicles need to be developed to improve their delivery properties [20]. Encapsulation of nutraceuticals in nanostructures such as food grade or GRAS, generally recognized as safe, resources still remains a challenge due to the previously stated problems regarding drug loading [21,22].

However, organic molecules have a complex structure that does not favor the formation of self-assembling nanoparticles without energy expenditure. The first type of nanoparticles synthesized from organic materials were nanomicelles (Nmcs) and nanoliposomes (Nlps), which are able to self-assemble due to their chemical nature [9]. In Nmcs, which are among the smallest organic NPs, the size is controlled by the length of the surfactant, and the smallest sizes to be achieved are that of a sphere with a radius equal to the length of the surfactant in the micellar phase, typically around 15–20 Å [23]. One of the most important applications of Nmcs and Nlps is drug delivery because the particles may contain insoluble substances within their cavity. However, size can influence the pharmacokinetics of nanoencapsulated drugs, including dosage [24]. Furthermore, natural nanoparticles show other advantages, such as reduced secondary effects on long-term use, and are preferred in antiviral or anticancer therapies [25].

Polymerizing molecules allow new types of nanoparticles, such as lipid nanoparticles, to be obtained by incorporating an insoluble substance and improving its delivery. Currently, in nanomedicine, the encapsulation of drugs in nanopolymers of about 200 nm is preferred [26,27]. Solid Lipid Nanoparticles include a solid lipid matrix, an emulsifier or surfactant, and the active compound [28]. Recently, Nebivolol-loaded lecithin-chitosan hybrid nanoparticles (NEB-LCNPs) having an average size of 170.5 ± 5.3 nm and a drug loading of 10.5 ± 1.2% were synthesized [29]. On the other hand, nanoparticles synthesized with mimetic and self-assembling peptides or polymers have been used to increase the specificity of a drug and, in turn, its potency [30]. Moreover, nanomaterials seem to have great potential for anticancer and antiviral therapy [31,32]. However, despite their nanometric size, drug-trapping nanoparticles are characterized by drug loading, a key parameter that affects their pharmacological efficacy. The drug loading parameter is defined as the mass ratio of

the drug to the drug-loaded nanoparticles. To our knowledge, nanoparticle systems entrapping or loading drugs have a relatively low drug loading (<10 wt%) [33].

For the above reasons, we are interested in formulating unencapsulated nanonutraceuticals with only a minimal amount of a capping agent. Two methodologies are possible to obtain nanoparticles, each involving chemical, physical, or biological techniques. The top-down method starts with the bulk powder, with a millimeter size, to obtain smaller nanoparticles. The techniques to reduce the dimension of granules include mechanical milling, nanolithography, arc discharge, electrospinning, sputtering, laser ablation, pulse wire discharge, sonication, and electron explosion. Inversely, the bottom-up approach starts with single units of atomic or molecular size to synthesize larger nanoparticles. These are: chemical vapor deposition, metal organic decomposition, laser pyrolysis, solgel, plasma arcing, molecular beam epitaxy, wet synthesis, controlled self-assembly [34]. Considering the size of the nutraceutical powders available on the market, we assessed the milling method as more cost-effective than others and scalable to an industrial level. Therefore, we studied its versatility to reduce the particle size of very different compounds by applying the same milling process to those substances.

In particular, here we present the results of our study on 90% rich acids from *Boswellic serrata*, N-acetylglucosamine, N-acetylcarnitine, Taurine and Homotaurine.

Boswellic serrata acids are a traditional herb extract used as anti-inflammatory agents. Some studies have shown that it has a protective activity in the case of osteoarthritis, and recently several pharmacological uses have been described [35,36]. As we are very interested in the treatment of osteoarthritis, we studied the activity of N-acetylglucosamine which is widely used as an anti-inflammatory and pain breaker in joint disorders [37]. On the other hand, N-acetylcarnitine is an amino acid very different from the other compounds and also its pharmacological effect. Recently, the use of N-acetylcarnitine has been described in the treatment of psychiatric disorders [38]. Taurine and its homotaurin dimer, which are functional amino acids, are also involved in neuropsychiatric pathologies. Both compounds target the $GABA_A$ receptor [39]. We believe that all studied compounds have so many differences that the production of their nanoparticles would require different protocols then to study one process for unrelated compounds is an interest of applied research.

2. Materials and methods

2.1. Chemicals and reagents

The powders of the nutraceuticals and surfactants used, certified for human use, were purchased from Galeno srl (Comeana (PO), Italy). In particular, we used 1) a dry extract of 90% *Boswellia serrata* acids and 10% uncharacterized mixture of triterpenes, diterpenes, monoterpenes, monosaccharides, and volatile oil; 2) pure N-acetyl-D-glucosamine (CAS 7512-17-6); 3) pure N-acetyl-L-carnitine hydrochloride (CA 5080-50-2); 4) pure Taurine (CAS 105-35-7); 5) pure Homotaurine (CAS 3687-18 -1), Polyvinylpyrrolidone (CAS 9003-39-8). Reagents for reactions and analysis,

if not specified, were purchased from Sigma Aldrich (Merck Spa), Mi, Italy. The powders are characterized by different granulometry as shown in **Table 1**.

Table 1. Granulometry of commercial powders as certified by producers.

Name	**Powders granulometry**
Boswellia serrata acids	100% < 80 mesh
N-acetyl-D-glucosamine	90% = 40 mesh
	10% > 40 mesh
N-acetyl-L-carnitine hydrochloride	90% < 20 mesh
	10% > 20 mesh
Taurine	36.38% < 80 mesh
	30.05% <120 mesh
	33.27% >120 mesh
Homotaurine	90% < 80 mesh
	10% > 80 mesh
Conversion from mesh to millimeters	
Mesh	mm
120	0.125
80	0.177
40	0.400
20	0.841

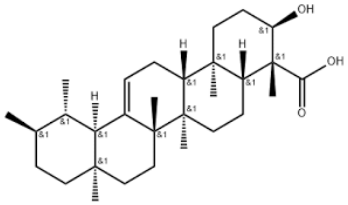
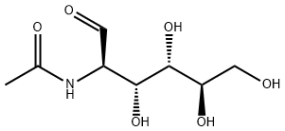
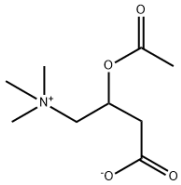
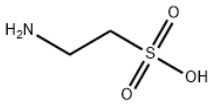
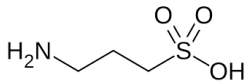
On the other hand, the nutraceuticals have different physical properties and chemical structures, as shown in **Tables 2** and **3**.

(PubChem release 2021.10.14) MW = molecular weight; XlogP3-AA = water partition coefficients; HBDC = Hydrogen Bond Donor Count; HBAC = Hydrogen Bond Acceptor Count; RotBC = Rotatable Bond Count; TPSA^{x}Å^{2} = Topological Polar Surface Area; HAC = Heavy Atom Count; Isotope AC = Isotope Atom Count; Defined ASC = Defined Atom Stereocenter Count; UASC = Undefined Atom Stereocenter Count; DBSC = Defined Bond Stereocenter Count; UBSC = Undefined Bond Stereocenter Count; CBUC = Covalently-Bonded Unit Count.

Table 2. Physical properties of the investigated nutraceuticals.

Compound	**Molecular WEIGHT g/mol**	**Xlog P3-AA**	**HBDC**	**HBAC**	**RotBC**	**TPSA Å^{2}**	**HAC**	**Formal Charge**	**Complexity**	**Isotope AC**	**Defined ASC**	**UASC**	**DBSC**	**UBSC**	**CBUC**
B. serrata acids	512.7	7.2	1	5	3	80.7	37	0	1060	0	11	0	0	0	1
N-acetyl-D-glucosamine	221.21	−1.7	5	6	2	119.0	15	0	235	0	5	0	0	0	1
N-acetyl-L-carnitine	203.24	0.4	0	4	5	66.4	14	0	214	0	0	1	0	0	1
Taurine	125.15	−4.1	2	4	2	88.8	7	0	120	0	0	0	0	0	1
Homotaurine	139.18	−3.8	2	4	3	88.8	8	0	133	0	0	0	0	0	1

Table 3. Chemical structures of the investigated nutraceuticals.

Name	Structure
Boswellic acids	
N-acetyl-D-glucosamine HCl	
N-acetyl-L-carnitine HCl	
Taurine	
Homotaurine	

2.2. Top-down preparation of nanoparticles

Regardless of the chemical structures and characteristics of nutraceuticals, the nanoparticle systems were obtained using 5 g of each powder inserted into a planetary ball mill operating at a speed of 800 revolutions per minute (rpm). The trituration was carried out by mixing each powder at the time with Polyvinylpyrrolidone (PVP) (99:1 w/w), and adding 50% (w/w) of balls. The reaction was carried out in 1 hr at 30 ℃. After centrifugation, the powder was recovered with a yield ranging from 88% to 96% (w/w) and stored in the dark and at room temperature for further use.

2.3. Dynamic light scattering

DLS and DELS measurements of the produced NPs were performed at 25 ℃ with a Zetasizer Nano apparatus (Malvern Instruments Ltd.) equipped with a 4 mW HeNe laser source (632.8 nm). The nanoparticles were dissolved in double-distilled water and filtered through a 200 nm filter before measurement. DLS autocorrelation functions were analyzed by the cumulative method to obtain the average sample size (hydrodynamic size) and polydispersity index (PDI) [40]. The intensity-weighted NNLS algorithm was used to determine the characteristics of the size distribution [41]. In DELS measurements, phase analysis light scattering (PALS) was used to obtain the ζ potential [42].

3. Results

3.1. Planetary ball mill

The top-down technology, made with a planetary ball mill, has allowed us to work with all types of studied powders using the identical process. For all the compounds studied, we took as a starting point the powders available on the market. For each compound, we directly mixed the powder with the same amount of PVP capping agent and processed them with a planetary ball miller. For all compounds, we use the same ratio between the powders and the balls. Polyvinylpyrrolidone (PVP) is one of the most commonly used polymeric stabilizers, due to its non-toxicity, amphiphilic character, and the presence of C=O, C–N and $–CH_2$ functional groups. After the process, the amount of dry powder recovered ranged from 94% to 97%. About 90% of the particle is constituted by the active ingredient with a considerable increase in biological potency. However, the average size of powder is slightly larger than 200 nm, a size considered acceptable for nanomedicine applications. The use of a single protocol to reduce different commercial powders to a nanometric size has allowed us to decrease the production costs. Furthermore, the study of the biological effects of some of the described nanoparticles showed unpredicted off-label activity. Nanotechnologies offer several advantages in medicine, such as the discovery of novel effects of known compounds and decreasing the volumes of powders and waste in the productive chain.

3.2. Dynamic light scattering analysis

The analysis of the grain size of the powders showed a reduction in their size at the nanometric with extremely small PDI values, suggesting that the powders can be considered even more homogeneous than commercial ones. On the other hand, the Z-potential data suggest that their distribution is also stable, as shown in **Table 4**.

Table 4. Average size powders after application of top-down methodology.

	compound	Z-average of nanoparticles (nm)	PDI	Z-Potential (mV)
1	*B. serrata* acids	433 ± 72	0.49 ± 0.03	−25.3 ± 0.8
2	N-acetyl-D-glucosamine	202 ± 6	0.38 + 0.02	−21.8 ± 0.3
3	N-acetyl-D-carnitine	304 ± 5	0.12 ± 0.01	−5.9 ± 0.1
4	Taurine	240 ± 14	0.23 ± 0.03	−14.3 ± 0.6
5	Homotaurine	439 ± 65	0.39 ±0.06	−11.2 ± 1.0

4. Discussion

Fine-tuning of nanoparticles properties, such as the size, is considered an important objective of nanotechnology to control the type of product and its application [43]. On the other hand, an ideal industrial process, among several needs, should be repeatable, scalable, have a good quantitative yield of product, not require much personnel, not last long, not consume too much energy, not produce too much waste, or consider the recovery of part of the material used. However, at an industrial level, the search for a very similar protocol capable of processing powders of very different substances can be useful to reduce production costs and waste materials and thus also achieve more environmentally sustainable processes. Among the

techniques of the top-down methodology, the most used are ball milling, thermal evaporation, laser ablation, and sputtering. The ball milling is a process where the movement of balls increases their kinetic energy. The collisions among balls and bulk material result in a size reduction of granules. Several types of technology are suitable for the ball milling, such as planetary mill, attrition mill, horizontal mill, vibratory mill, and rotatory mill. The impacts are mainly elastic or quasi-elastic when a fraction of powder blends with the surface of the balls. These techniques have both advantages and disadvantages, which depend on the purpose of desired nanoparticles. The advantage of ball milling is that the process is carried out by a mechanical machine that induces the high kinetic energy of balls; in turn, the attrition among balls and powder yields the fracture of the bulk into nanoparticles. The process can be controlled by one operator, can be done at room temperature, and also uses an uncontrolled atmosphere. Among disadvantages, the process may require the use of a solvent, and to obtain dry powder, there is an energy expenditure. Furthermore, in the case of organic material, it is very difficult to reach the nanoscale below 100 nm. All types of ball milling techniques have industrial advantages: the machines are not expensive, the process is mechanical and it can be controlled by one operator, it is scalable, and it does not use toxic solvents. On the other hand, there are some disadvantages, as the process takes some hours to be completed, and it is difficult to reach the nanometric scale and regular shapes [44].

Thermal evaporation is apparently an economical technique to vaporize the material and induce its deposition onto a substrate under vacuum conditions. The system is suitable for obtaining thin layers rather than producing a powder for the pharmaceutical formulation of a drug. However, the energy expenditure becomes a disadvantage if the starting material has low thermal and electric conductivity. The process is generally used for inorganic bulk. The plant is not easy to operate and requires an experienced operator. Moreover, the process does not seem easy to scale to large quantities, and large vacuum chambers are expensive [45].

The laser ablation requires an expensive laser system to induce evaporation of atoms by the surface of the material. This technique yields high purity and very small nanoparticles, but it is expensive on an industrial scale and requires a team of expert operators to complete the process [46].

The sputtering is a process through which microscopic particles of a target material get ejected from its surface after the bombardment of energetic ions of gas or gaseous plasma. Momentum exchange between atoms and ions of the element causes sputtering. It has a high advantage in fine-tuning the nanoparticle's properties, but it is the most expensive at an industrial scale, and it requires the use of gaseous solvents [47].

As regards the bottom-up methodology, there are: chemical vapor deposition, hydrothermal, co-precipitation, sol-gel. The vapor deposition can be physical or chemical deposition, depending on the approach, and there are different techniques suitable for different substrates [48]. The chemical vapor deposition is typical within the bottom-up method to synthesize nanoparticles. The advantage is that it enables a higher-purity surface coating, and it is scalable at an industrial process. Among the disadvantages, the method is not suitable for organic molecules, which could be modified by the chemical reactions. However, the chemical vapor deposition yields

two-dimensional surfaces, and the method is expensive, and it is not common to synthesize organic nanoparticles [49,50]. The Hydrothermal techniques can require strong ionic conditions, such as alkaline, and high temperature that affect the structure of an organic compound so that hydrothermal synthesis is not suitable for the pure organic nanoparticles [45].

The coprecipitation techniques involve solubilization of the bulk material in a solvent, followed by addition of an anti-solvent at a specific rate under constant stirring to obtain the precipitation of nanoparticles. The process needs a growth mechanism of the agglomerate followed by a nucleation and anisotropic growth of single crystals of desired size. Generally, when the concentration of substances reaches supersaturation, a nucleation suddenly appears in solution. The technique is simple and can yield very small nanoparticles, can be controlled by a single operator, and is suitable for scale-up. However, the main disadvantages require the use of solvents, which can be toxic and must be removed; after a dryer, which consumes energy, is required to obtain the powder [51].

The sol-gel technique is a wet chemical process to synthesize nanoparticles starting from a molecular precursor dissolved in water or alcohol and converted to gel by heating and stirring by hydrolysis/alcoholysis. Since the gel obtained from the hydrolysis/alcoholysis process is wet or damp, it should be dried under appropriate conditions to obtain the desired gel. The sol-gel method is a cost-effective method that takes place through a low-temperature reaction. There is good control over the chemical composition of the products. Although it has more than one advantage, it is not described for the synthesis of pharmacologically active ingredients [52].

All five studied compounds have many differences, but they have some similar physical features, such as their formal charge being zero, suggesting that the molecules have a similar distribution of electrons. All compounds have no stereogenic or stereochemical centers as suggested by their DBSC and UBSC values. Our results show that planetary ball milling is reasonable to produce nanoparticles starting from different compounds.

5. Conclusion

The production of nanoparticles from organic compounds suitable for pharmaceutical applications is an important objective of the chemical-pharmaceutical industry research. Although there are several techniques, some fundamental problems remain to be solved, such as the scalability of the method, the number of skilled workers to manage the process, the cost of the plant, energy consumption, the type and quantity of solvents to be used, the size of the nanoparticles, and the surface homogeneity of each nanoparticle. A top-down approach may be appropriate if the objective is to produce nanoparticles starting from raw material currently used in the chemical-pharmaceutical industry. The machines to produce, at an industrial scale, the friction between balls and powders are cost-effective. Furthermore, the ball milling process can take place at room temperature and in an uncontrolled environment. It can also be run by unskilled personnel and, in our conditions, does not seem to depend on the type of starting compounds. The results of this work relating to the comparison of different powders

and corresponding nanoparticles, obtained using the same protocol, demonstrated that the planetary ball mill is able to reduce the size of commercial powders by a factor of 10^3 and that it is difficult to assess a difference in the size of the particles [53]. Interactions among particles are important in pharmaceutical engineering because they take into account the forces that tend to keep adjacent particles fixed in their relative position. These interactions have been associated with the size, shape, and surface characteristics of the granules, so the availability of a known particle size of the nanoparticles allows a new approach to pharmaceutical formulations. On the other hand, the presence of PVP, which is associated with N-acetylglucosamine with weak forces, should be considered. In our formulations, however, PVP is a minimal percentage, but the compound has been shown to stimulate cell proliferation [54]. Previously, we showed that nanotechnology increases the biological potency of N-acetylglucosamine [53]. Therefore, nanotechnology applied to well-known compounds can represent a great advantage for medicine and the pharmaceutical industry.

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