Nano Spray-Drying: a Reliable Modern Approach for Drug Carriers Development

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Abstract. For several decades nanosized systems are object of interest, the characteristics that makes them attractive drug carries systems are well known. One of the main advantages of the nanoparticle drug delivery systems, are their small sizes, that allows penetration trough some biological membranes and entering target tissues, especially nanoparticles conjugated with different ligand. In addition, depending on the technique of encapsulation, the drug loading efficacy and the biopharmaceutical behavior are improved. There are several methods for obtaining nanoparticles – emulsification-solvent evaporation method, emulsion solvent diffusion method, salting out, polymerization and polycondensation methods. Their process parameters can widely affect particle characteristics, like particle size, size distribution, zeta potential, structural and morphological characteristics, drug encapsulation and biopharmaceutical behavior. The technological progress in recent years resulted in improvement of the production equipment and led to achieving promising results, true the method of nano spray drying. This method is based on transformation of solution, emulsions and suspensions in dry particles, with different structure and properties, allowed controlled and safe production of nanosized structures, preservation the molecular activity due to gentle process conditions.The method is single step, easily accessible and ensures high yield with minimal production losses. The aim of this study is to present in details the method of nanospray drying and to systemize the data for the influence of different process parameters to the structural and morphological characteristics of the nanoparticles and their biopharmaceutical behavior.

Keywords: nanoparticles, targeted therapy, spray drying

1. INTRODUCTION

Nanoparticles are described as solid particles, within the size rage from 10 nm to 100 nm. They are used in different fields of technology – food, engineering, and pharmaceutics. Nanoparticles intended for drug delivery are designed from macromolecular assemblies in which the drug is dissolved, encapsulated or absorbed into the external surface. As a drug delivery system, they enhance the absorption rate, improve bioavailability and enable targeted drug delivery for cancer therapy. Based on their morphology, nanoparticles can be classified into two large groups: nanospheres – metrical structures in which the drug is dispersed, and nanocapsules – core-shell structures. There are certain challenges that make the fabrication of nanoparticles very difficult – size, surface morphology, particle size distribution and therapeutic goals, as well as biocompatibility of the polymer. Different methods are involved for the production of nanoparticles, namely physiochemical, chemical and mechanical methods. Physicochemical methods result into the formation of nanoparticles often using polymers as wall materials, or by precipitation using emulsification-solvent evaporation, diffusion or reverse salting out techniques. Mechanical methods for nanoparticles preparation include the use of high-energy wet mills, high-pressure homogenizers, and sonicators.

2. SPRAY-DRYING TECHNIQUE FOR PARTICULATE FORMULATION

Spray-drying is an innovative, simple, fast and reproducible drying technology for obtainning nanoparticles. It is well-established method in food, chemical, and pharmaceutical

industries (Bürki et al., 2011; Vehrring et.al, 2008; Wang et al., 2005; Wendel and Celik, 2005). This technique is based on the transformation of various liquids (solutions, emulsions, and dispersions) into solid particles of different size, shape, density, chemical composition and distribution (Arpagus and Schwartzbach, 2008). This technique is used for drug encapsulation into different types of materials. Encapsulation protects active pharmaceutical ingredients against harsh environmenttal conditions, and can provide drug delivery to a specific site in the body acomplishing targeted therapy (R.Vehring, 2008).

Traditional spray drying technique is based on heating the drying gas, droplet generation, drying the droplets and particle collection. Compared to other methods of nanoparticle preparation, spray drying method has numerous benefits: control of particle size, shape and morphology; easy, one-step process with easy operation at a low cost; processing heat-sensitive substances (Wong and John, 2015).

3. NANO SPRAY DRYING FOR NANOPARTICLE PREPARATION

A novel method for the preparation of nanosized drug delivery systems is nanospray drying. Nano spray drying enables the formation of smaller particles below 1 000 nm, which improves drugs biopharmaceutical characteristics. Compared to other drug delivery systems, drug-loaded nanoparticulate delivery systems offer various advantages, such as higher surface-volume ratio, higher penetration rate into cells, improved stability and possibility for targeted therapy.

Particle formation using nanospray drying can be described as a complex process which combines solvent evaporation and diffusion of aqueous and organic solvents with formation of droplets because of the simultaneous heat and mass transfer (Vehring, 2008). The drug solution is dispersed in fine droplets, then the solvent evaporates, the droplets shrink and a fine powder is formed. The final powder structure can be amorphous or crystalline, and the particle size is within the nanoscale range.

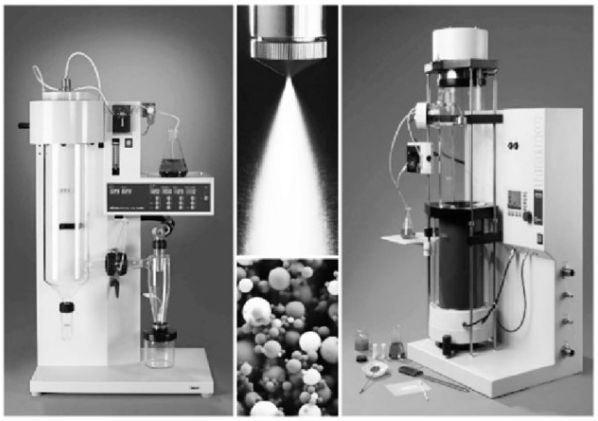

Fig. 1. Spray drying techniques.

Spray drying method is also used for transformation of particle morphology, thus improving hydrophobic drugs poor water solubility (Li et al., 2010; Martena et al., 2012). In nanoencapsulation, drug solution is encapsulated into a solid matrix. To form nanocapsules, oil-in-water nanoemulsion is entrapped in a matrix formed by different polymeric materials. The oil phase serves as a reservoir for hydrophobic drugs (Rajabi et al.,2015, Sabilov and Astete, 2015). The emulsion is mixed with the solvent and binders (polymeric materials), then it is sprayed into small droplets, the solvent is evaporated leaving solid matrix around the hydrophobic phase of the emulsion. The obtained small droplets are stored in the carrier solution. Capsules smaller than 1000 nm are described as nanocapsules (Arpagaus et al., 2017; Couvreur et al., 1995).

4. NANOSPRAY DRYING EQUIPMENT – PRINCIPLES AND APPLICATIONS

For the production of nanoscale particles using a spray drying technique, certain modifications of the drying technology are required. Particles of submicron range cannot be collected with traditional cyclone separators and even with high-performance glass separators. A feasible approach to collect the fabricated nanoparticles is using electrostatic collectors (Heng et al., 2011; Li et al., 2010). Traditional atomizers do not allow the generation of very fine droplets and the formation of submicron particles. Furthermore, the turbulent gas flow in the drying chamber

can lead to increased particle deposition on the chamber wall. Advantages of the nanospray dryer technology and the introduction of the Nano Spray Dryer B-90 by Buchi Labortechnik AG (Switzerland) in 2009 have made it possible to produce nanoparticles via spray drying technique (Arpagus et al., 2018).

Fig. 2 Nano spray dryer Buchi B-90.

The fine droplets are produced due to the innovative vibrating mesh technology (Knoch and Keller,2005; Lass et al., 2006). The spray nozzle is connected to a piezoelectric actuator that vibrates at ultrasonic frequency (80-140 kHz). Attached to the nozzle is a small spray cap, which consists of a thin perforated metal plate, containing a series of tiny laser-drilled holes. The piezoelectric vibration generates up and down movement of the spray mesh. That leads to the ejecting of millions of precisely sized droplets through the holes into the drying chamber. The droplet size depends on the physicochemical properties of the fluid, such as viscosity and surface tension. The size depends also on the mesh size (Schmid et al., 2011; Arpagaus et al., 2010).

The drying gas is heated up to the required inlet temperature. The gas directs the formed submicron particles to the electrostatic particle collector. Due to the electrostatic charging of the dried particles, they are collected at the collecting electrode (Lee et al., 2011).

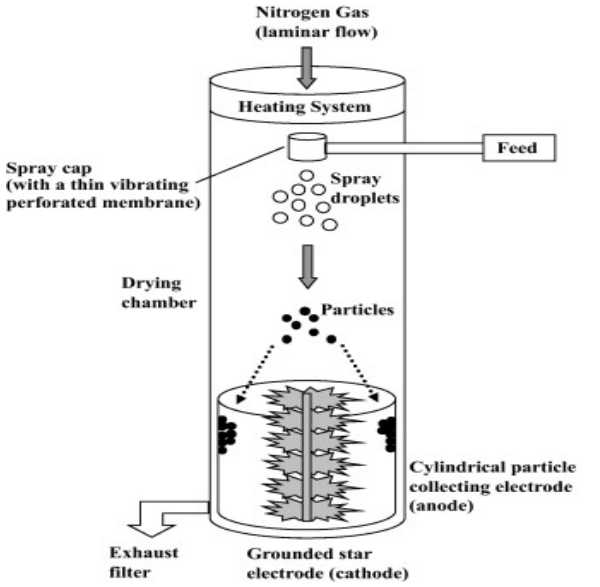

Fig. 3 Mechanism of nanoparticle formation using nano spray drying technique.

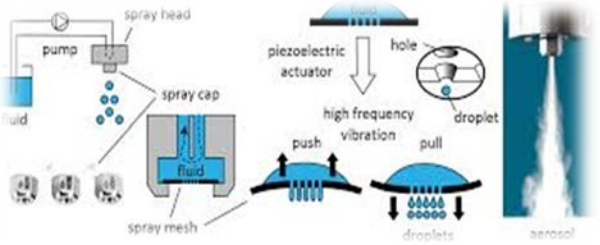

Fig. 4 Formation of ultrafine nanoparticle powder.

Nanospray drying technique is suitable for gentle drying of heat sensitive products, because of the laminar flow of the drying gas. That high voltage enables the recovery of submicron particles at a separation efficiency of more than 99% (C.Arpagaus et al., 2018, Feng et al., 2011). Variations in the yield can occur due to the manual scraping of the powder. The recommendation of the manufacturer is that the collection must be performed in a controlled and dry atmosphere. The obtained particles must be stored in a desiccator at room temperature (Schmid, 2011)

5. FACTORS AFFECTING NANO-SPRAY DRYING EFFICIENCY

The most important process parameters, that affect the properties of nanoparticles, obtained true the nano spray dring technique

are shown in Fig. 1. As it is shown in Table 1, the product properties (droplet size, particle size, moisture content, yield, and stability) depend on the process parameters. Key parameters affecting the particle size are the spray mesh size, spray rate intensity, the concentration of the drug, surfactant, and stabilizer. The use of larger spray mesh sizes, increase of the spray intensity and more concentrated solutions leads to the formation of larger nanoparticles. Smaller droplets are obtained by increasing the concentration of the surfactant and stabilizer, also using solvent different from water also decreases the particle size (X. Li et al., 2010).

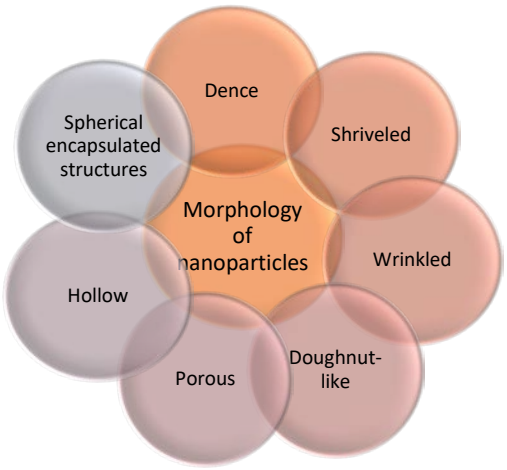

Fig. 5 Process parameters affecting orphology of nanoparticles.

Table 1 Process parameters.

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

Compared to water, organic solvents generate smaller droplets due to the lower surface tension, viscosity, and density (Survaprakash et al., 2014). Organic solvents enable lower drying temperatures and prevents from particle agglomeration (Heng et al., 2011).

The outlet temperature is controlled by the drying flow rate, inlet temperature, and the spray rate intensity. Lower drying gas flow rates lead to lower outlet temperature. When the feed rate is smaller, the outlet temperature is higher, because of the higher moisture content, depending on the fluid evaporation. Higher inlet temperature reduces the moisture

content and the formation of dried powder with less stickiness (Feng et al., 2013).

The feed rate increases due to the spray mesh size, spray rate intensity and the pump rate. It is defined that when using aqueous solutions and 4,0 μm spray mesh size the feed rate may range from 3-25 mL/h (Li et al., 2010). As shown in previous studies, higher solid concentration leads to a lower feed rate. The feed rate is about 50 mL/h when spray drying 0.1 % (w/v) chitosan solution in 1 % (v/v) acetic acid trough 5.5 μm spray mesh size (Gautier et al., 2010).

6. MORPHOLOGY OF NANOPARTICLES

The morphology of the obtained nanoparticles depends on the drying conditions and the feed properties. Based on their morphology nanoparticles can be categorized in several groups (B. H. Zainudin et al., 2018).

The slow drying process leads to the formation of more compact particles, while fast drying at high temperature leads to the generation of more hollow particles (Feng et al., 2011; Arpagaus et al., 2018).

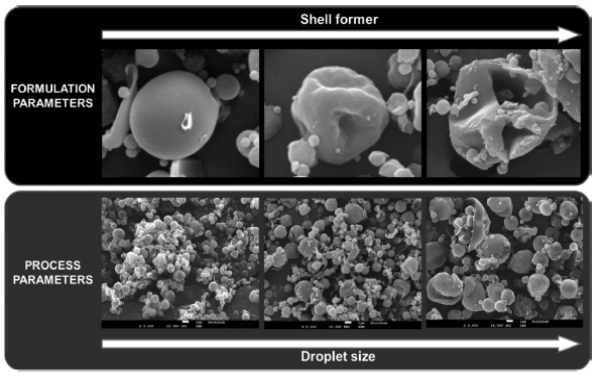

Fig. 5 Effect of the production parameters to the morphology.

The generation of smooth and spherical particles is accomplished by the addition of surfactants. Shriveled and wrinkled particles are common morphologies for larger particles produced from surfactant-free solutions. Doughnut-like particles are formed because of the hydrodynamic effects and the loss of structural stability of the droplets (Dahlili et al., 2015; Lee et al., 2011).

7. ENCAPSULATION OF DRUGS USING NANOSPRAY DRYING TECHNIQUE

Nano spray drying is used for the formation of pharmaceutical dosage forms to transform solutions, suspensions, emulsions into dry nanosized particles. Nano spray drying is a novel, widely used method for obtaining drug-loaded nanoparticles, used as drug delivery systems for the treatment of various diseases, such as tuberculosis, asthma, inflammations, diabetes, ophthalmic disorders, high blood pressure, and cancer (C. Arpagaus et al., 2018).

Common advantages of nanoparticles as drug delivery systems include huge surface area, high drug loading capacity, capacity for functionalization with ligands, controlled drug-release, minimal toxicity, biocompatibility, high stability, and different routes of administration. Despite the numerous advantages, nanoparticles have some drawbacks that must be overcome before application. Some of these limitations include easy recognition by the mononuclear phagocyte system, a short period of circulation in the bloodstream and low drug uptake because of the abnormal tumor structures (B. H. Zainudin et al., 2017).

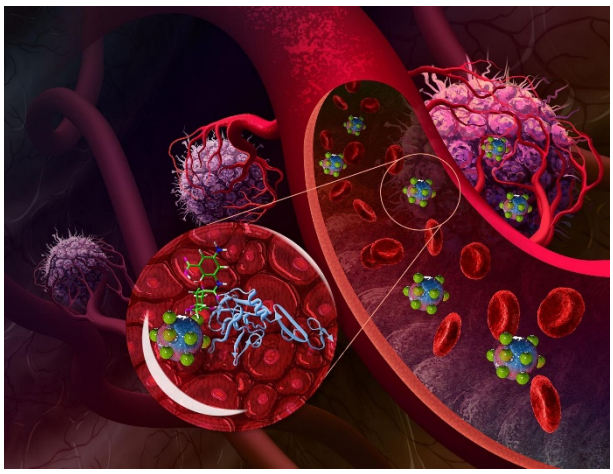

Fig. 6 Nanoparticles targeting cancer cell.

Functionalization of nanoparticles with different ligands overcome these challenges and lead to the possibility of target therapy. There are two major tumor-targeting strategies – passive and active targeting. These two

strategies correlate one another and deliver the drug to the target site. With passive targeting, the drug is delivered to the specific target site using pathophysiological changes of the cancer tissue. Active targeting leads to receptor-mediated internalization of the nanoparticles into the tumor cell. Targeted therapy is used for the treatment of breast cancer, colorectal cancer, lung cancer, melanoma and different types of lymphomas. (C.Arpagaus et al., 2018; X.Li et al., 2010).

Nanoparticles can be conjugated with different biological molecules. Depending on the structure and properties of the conjugated molecule, nanoparticles can be targeted to specific sites in the body. There are numerous polymers used for the preparation of nanoparticles.

8. BIOPHARMACEUTICAL PROPERTIES OF NANO SPRAY DRIED NANOPARTICLES

There are various routes of drug administration (oral, pulmonary, topical, parenteral, etc.). Spray-dried nanoparticles loaded with active pharmaceutical ingredients are in the form of fine powders. These powders may be used for the preparation of solid or liquid dosage forms. After oral administration, nanoparticles should enter the systemic circulation. This is restricted by the acidic environment in the stomach, the protease activity in the gut lumen and the presence of liver enzymes (Harsha et. al., 2013). Nanoparticles must be mucoadhesive to pass and penetrate from the epithelial cells to the bloodstream. Upon entering the systemic circulation, nanoparticles reach the specific target site of action and release the drug by several mechanisms – dissolution, osmosis, diffusion, swelling, and erosion. The size, shape, surface charge and molecular weight play a major role in the release and bioavailability of drugs. The prolonged circulation and accumulation in the targeted tissue and enhanced diffusion can be obtained by the use of nanoparticles with size from 20 to 100 nm. According to a research performed by Beck-Broichsitter et al. (2015), smaller particles exhibit higher speed of release compared to larger ones, due to differences in the surface area (C. Arpagaus et al., 2018). The release kinetic is influenced also by the molecular weight of the polymers. As it is shown in a research performed by (Panda et. al., 2015), the release kinetic is higher in models with low molecular PLGA, than models in with PLGA with high molecular weight.

9. CONCLUSION

Compared to the traditional spray drying technique, nano spray drying method relies on innovative spray mesh technology, a patented airflow system for gentle solvent evaporation and a highly efficient electrostatic collector to produce ultra-fine powders containing nanosized structures. Using this method, different particle morphologies can be obtained – dense, hollow, spherical, wrinkled, shrank or donut-shaped. The particle properties – size, morphology, yield, drug loading, release kinetics, and encapsulation efficacy depend on the process parameters of the method, like inlet temperature, drying gas flow rate, mesh size, the concentration of stabilizers and polymers. Nano spray drying is widely used in the field of pharmaceutics to increase the bioavailability of poorly soluble drugs by encapsulation in polymer nanoparticles.

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