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Advances in Spray Drying for Pharmaceutical Formulations: Enhancing Drug Solubility and Bioavailability

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Abstract: Spray drying is a cutting-edge pharmaceutical technology that improves the solubility, dissolution rate, and bioavailability of drugs that are poorly soluble in water. In a typical spray drying cycle, a liquid drug solution is converted into fine droplets, which are instantly dried to form solid particles. The resulting amorphous solid dispersions provide much better stability and dissolution attributes for the drugs than their crystalline forms. Spray drying enables the development of controlled-release formulations for inhalable drugs, as well as those delivered by nanoparticulate drug carriers. In addition, this method is cost efficient and easily scalable. Other traditional solid dispersion techniques, like freeze-drying and hot-melt extrusion, do not allow the incorporation of multiple excipients as easily onto the drug substance, providing the technological edge to the spray drying method. While spray drying offers some benefits, it is not devoid of weaknesses including thermal decomposition, leftover solvents, and the sticking of particles that can compromise the quality and stability of the product. It is crucial to consider several factors such as the composition of the feed, efficiency of atomization, temperature during drying, and the flow of air while optimizing the process. Improvements to formulation stability and manufacturing performance have become easier with advancement in material science and optimization of procedures. With the improvements being made with the research of pharmaceuticals, this method of spray drying continues to be useful for producing new systems of drug delivery with more treatment benefits and more usefulness in modern medicine.

Keywords: *Spray Drying, Solid Dispersion, Bioavailability, Drug Solubility, Pharmaceutical Formulations, Amorphous Solid Dispersion, Controlled Release, Dry Powder Inhalers, Nanoparticle Formulation, Process Optimization.*

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I. INTRODUCTION

Spray drying is common in the pharmaceutical industry as a means of improving a drug's solubility and bioavailability, especially for water-insoluble medications. The method works by turning the drug and carrier solution into a mist, which is then dried in a hot gas stream to form solid particles. This method produces amorphous solid dispersions, which enhance the rate of drug dissolution and stability relative to the crystalline form[1-2].

Compared with freeze drying and hot melt extrusion, spray drying is more scalable, economical as well as more uniform in producing powders with good flow properties. Furthermore, spray drying is particularly useful in the formulation of inhaled pharmaceuticals, polymer controlled release systems, and polymer dispersions. Nonetheless, the quality of the output is dependent on the mitigation of thermal degradation, residual solvent content, and particle adhesion to the walls of the spray dryer.[3-4].

II. ADVANTAGES

- **Fast Solvent Evaporation**- Evaporation of solvent takes place very fast in spray drying, which leads to rapid transformation of API-carrier solution into solid particles of API-carrier. Spray drying also helps in the formation of amorphous solid drug dispersions, hence increasing the drug solubility.

- **Enhanced Drug Dissolution and Bioavailability**- The amorphous solid dispersions that are produced by spray drying has higher rates of dissolution as compared to when they are in crystalline form. This enhances the bioavailability of poorly soluble drugs significantly.

- **Processing of Thermolabile Compounds**- Because spray drying is a solvent mediated process, it helps in the formation of solid dispersions without the need to put the drug under heating conditions, making it suitable for thermolabile drugs that are likely to be destroyed when

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subjected to heat.

- **Scalability and Continuous Manufacturing**- This method of spray drying is relatively easy to scale up, hence it can be used in small scale formulation development and large scale production of dosage forms. It is also suitable for continuous manufacturing which enhances productivity and uniformity.

- **Versatility in Formulation**- This method allows the use of a wide range of excipients such as polymers and surfactants that can stabilize amorphous solid dispersions and enhance drug dissolution. It also has a broad scope of solvent systems, which enables.[5]

III. DISADVANTAGES

- Residual Solvent Content Recovery of residual solvents after the solution is sprayed is a two-phase process. Residual solvent may pose a threat to the stability and safety of the final product if not controlled adequately.

- Poor Flowability All spray-dried powders have difficulties in flow characteristics, which affects widening of use in production processes. This causes a loss of productivity and reproducibility in dosage forms.

- Low Stickiness because of Low Glass Transition Temperature Some ASD formulations having low Tg can be sticky, causing difficulties in handling, storing and processing the powder due to loss of stability.

- Instability Potential due to Downstream Processing The structure of solid dispersions that have an amorphous state is prone to recrystallization or degradation from the forces of compression, coating or encapsulation which lowers the efficacy of the drug.

- Challenges Posed by New Chemical Entities (NCE) It is common for new drug compounds to demonstrate poor solubility in both water and organic solvents making selection of appropriate carrier systems very difficult for spray drying process optimization.[5]

IV. CHALLENGES

One of the most important problems is the storage phase stability of ASDs. Amorphous drugs have a tendency to undergo recrystallization with time, which will greatly affect their dissolution and solubility. To achieve the long-term stability of ASDs, appropriate polymer carriers and favorable storage conditions are necessary.

Attempts to form an ASD also raise issues concerning manufacturability. The two main methods used are spray drying (SD) and hot-melt extrusion (HME) but both have drawbacks. For example, HME is more suitable for commercial scaling of the product, but requires a large amounts of API, which is problematic in early stage research. On the other hand, SD is commonly used in discovery research because it can be done with very low amounts of API, however, it requires the use of organic solvents which poses issues of residual solvent, worker exposure, and environmental pollution.[7]

V. SPRAY DRYING PROCESS

- Spray drying is the simple process of transforming a liquid source into powder by the process of drying. The method is especially useful for the heat resistant materials because it limits the thermal degradation. This method is common in the pharmaceutical, food, biotech and chemical industries, which need tight control of the particle size, moisture, and flow rate.

- When spray drying begins, the first step is always the solution preparation. The product to be dried can be found in solution, suspension, or emulsion form and must be evenly distributed. The feed is filtered through homogenization to remove large particles or air bubbles which assist in creating uniform droplets when atomization occurs.

- The next step involves atomization which changes the liquid feed into small fragments of drop using an atomizer or nozzle. Depending on the application, atomizers can be pressure nozzles, ultrasonic atomizers or rotary discs. This stage is the most important one as it will decide the size of the particles.Subsequent to atomization, the oversprayed spherical particles undergo drying due to being passed through a hot drying chamber that exposes them to hot gas or air. The tiny droplets undergo rapid evaporation of water and they dry out within a few milliseconds due to the tremendous surface area of the small droplets. Temperature and airflow need to be controlled accurately because of the risk of overheating, especially for pharmaceuticals, proteins, and food products that are sensitive to excessive heat.

- After the solution is put through the dryer, the solid pieces are collected from the gas stream. The dry powder is collected using a cyclone separator, bag filter, or electrostatic precipitator while the clean air is passed through filters to capture dust particles. The collected powder can then undergo additional operations like blending, granulation, or encapsulation depending on application purpose.[8]

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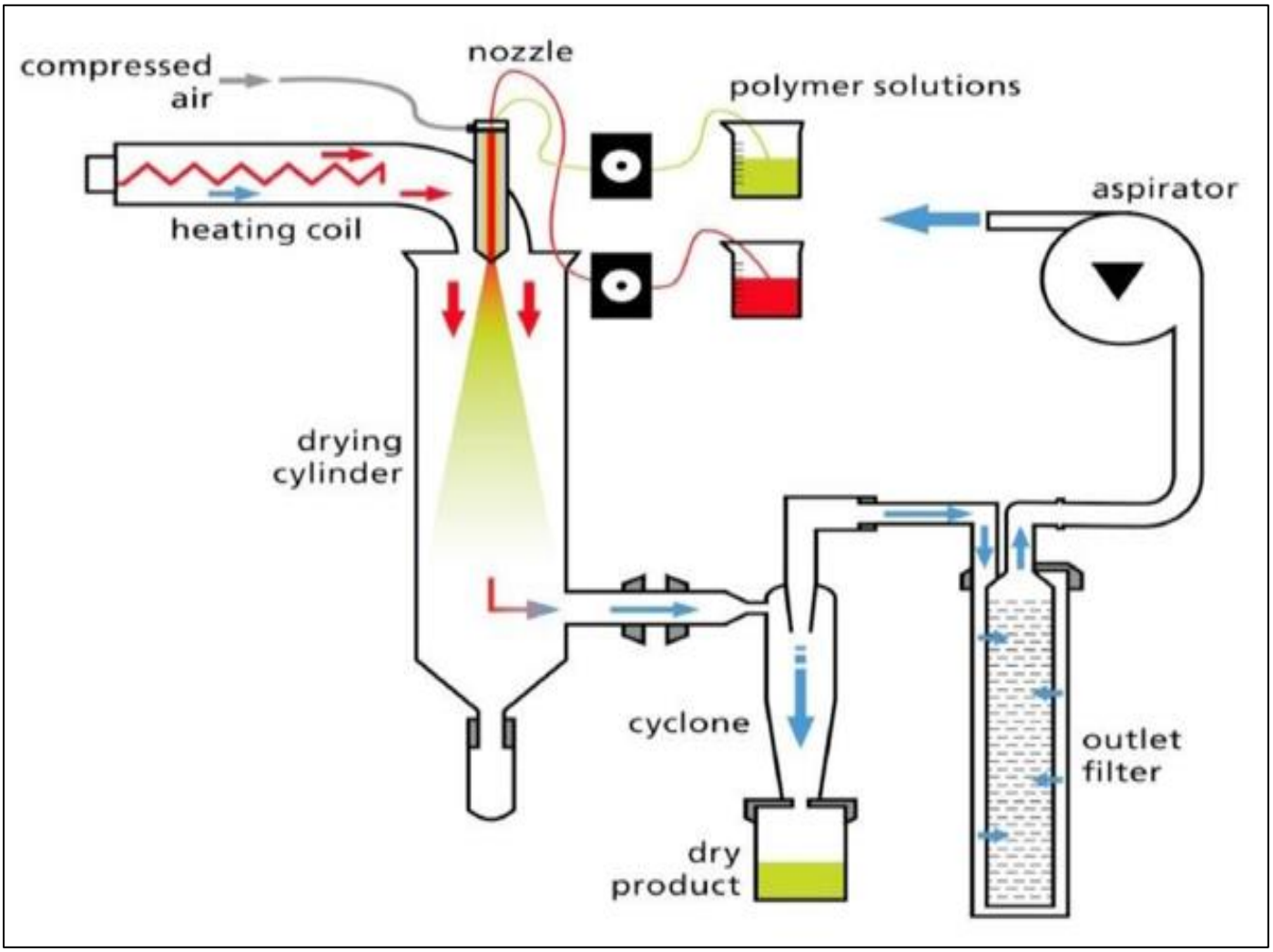

Fig 1 Different Parts of Spray Dryer.

VI. EQUIPMENT TYPES AND SCALES IN SPRAY DRYING

The designs of spray drying plants differ in many areas including type, capacity, level of automation, the type of gas used for drying, etc. The plant design choice is based on the product type, required particle size, production volume, and the intended application. From pharmaceutical solutions to food-grade emulsions and even chemical suspensions, spray dryers have the ability to process many types of feed materials.

➢ *Open Cycle Spray Dryers*

- The most widely employed systems are these ones, where the evaporating gas (mostly air) is taken from the environment, put through a heating cycle, and is released after stronger evaporation occurs.
- These solutions are appropriate for water solutions and non-volatile solvents. These are more typical in foods, dairy products, and the pharmaceutical industry.
- Closed Cycle Spray Dryers
- In such a system the drying gas is captured after the process is finished (which can be nitrogen or argon in that case). This makes them the preferred choice when dealing with oxygen-sensitive organic solvents or products.
- These dryers minimize the escape of solvents and are significantly safer in situations when flammable or toxic materials have to be processed.

➢ *Semi Closed Cycle Spray Dryers*

- These combine features from both, open and closed systems that restrain the total exhaust emission release while burning some type of drying gas further increasing energy efficiency.
- They usually cater to pharmaceutical and biotechnological activities that need temperature control.

➢ *Two-Stage Spray Dryers*

- These systems incorporate fluidized beds that act as a primary and secondary drying chamber to facilitate moisture removal.
- They are suitable for delicate heat-sensitive material, and offers enhanced control of particle size and moisture content.
- Equipment Scale and Production Capacities
- There are different types of spray drying equipment based on the size; from lab scale to dry powdered industrial plants.

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➢ *Laboratory-Scale Spray Dryers*

- For use in research, product formulation and development, and testing of products.
- Usually use small batch quantities, from grams to a couple of kilograms.
- Perfect for pilot runs of nanoparticles and drug formulations.

➢ *Pilot-Scale Spray Dryers*

- Serves as a bridge between laboratory scale and large scale commercial production.
- Great for rationalizing drying parameters, formulation and scale up procedures.
- Used for mass production of dried powder, capable of handling hundreds/thousands of kilograms per hour.
- Spray driers with modern automation, in-process measurement, and mass atomizers are equipped for use in the pharmaceutical, food, chemical.
- Considerations for Choosing Spray Dry Equipment There are numerous factors that determine the selection of a particular piece of spray drying equipment, including: Properties of the feed material (temperature sensitivity, viscosity, and solubility). Desired size of particles and amount of water present. Environmental concerns and energy costs. Regulatory requirements (particularly in food and drug manufacturing). Level of automation achievable and cleaning simplicity (important for product safety and contamination reduction).[9]

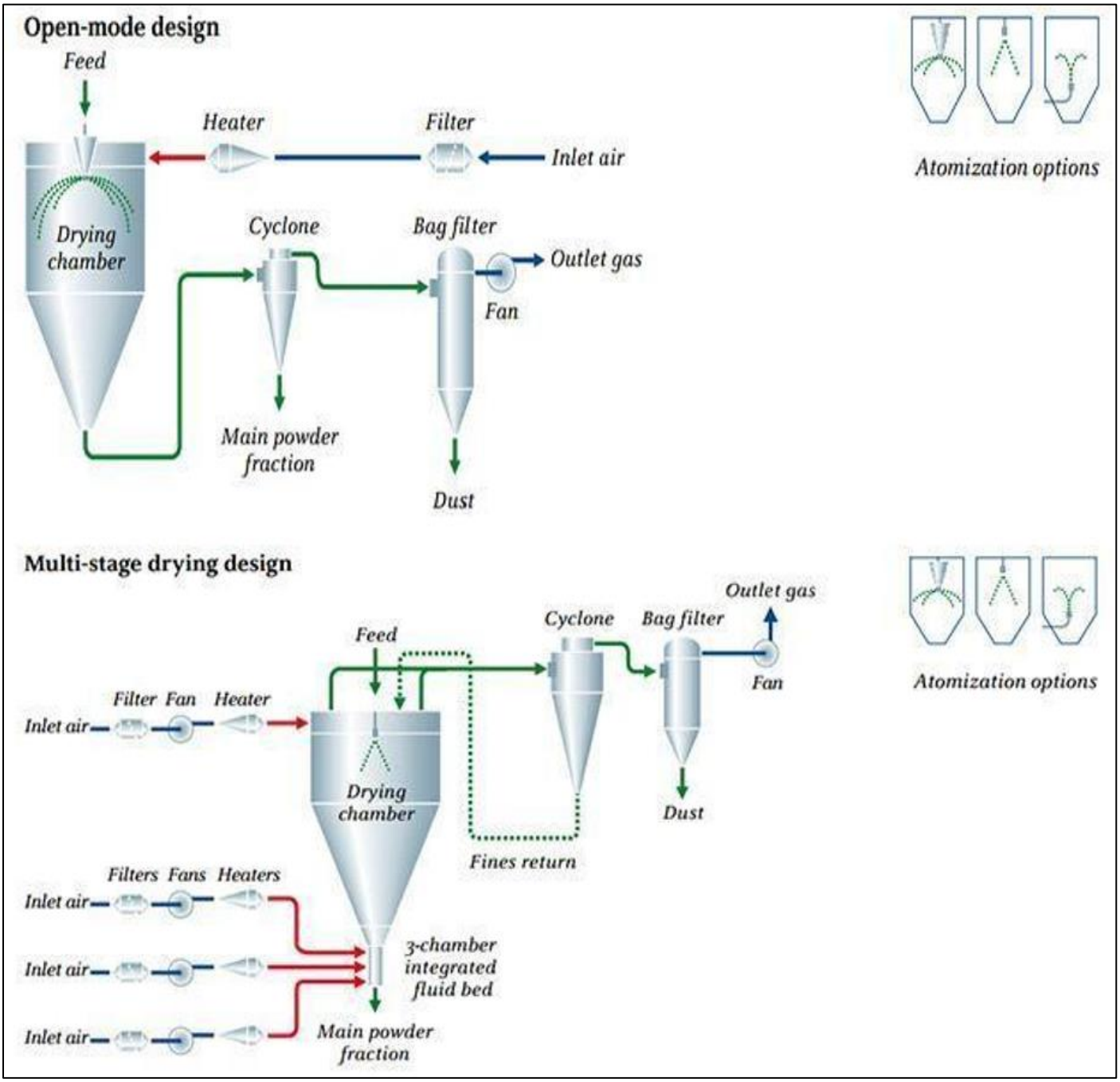

Fig 2 Different Process Layouts of Spray Dryer.

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VII. APPLICATIONS OF SPRAY DRYER IN PHARMACEUTICAL FORMULATION

- Spray drying remains one of the most preferred methods for producing matrix microcapsules with drug substances to achieve controlled drug release. Spray drying is used in microencapsulation because it can be adapted to different systems such as microspheres and microcapsules depending on the
- type of aqueous solution (e.g., solution, suspension, or emulsion) used as a starting aqueous formula. A microcapsule can be thought of as either a single solid particle or liquid droplet that has been coated, or as a matrix containing several fine core particles. [10-11]
- Example: Sustained-release theopylline tablets as well as enteric tablets, were created by direct compression of Eudragit L30D, L100-55, and E30D microspheres. Other products such as microparticles of diltiazem hydrochloride were also produced using the spray drying method along with coating agents like Eudragit RS and Eudragit RL acrylate-methacrylate copolymers.
- To develop controlled-release solid dosage forms, acetaminophen loaded binary microspheres made with Eudragit® RS and RL and ethylcellulose polymers were prepared using co-spray drying method with several ratios of drug to polymer (1/2, 1/1, 2/1, 3/1, 4/1, 6/1, 9/1, 19/1).
- The purpose of spray drying is to enhance solubility and dissolution rates of poorly soluble drugs through the formation of pharmaceutical complexes or solid dispersions to improve bioavailability.
- Low solubility molecules may demonstrate absorption that is limited by dissolution rate, and consequently, poor absorption, distribution, and delivery of the drug to the different organ systems may occur. Developing water solubility in these compounds serves to enhance therapeutic value. Spray drying complexation has been shown to increase the degree of solubility, dissolution rate, and bioavailability of poorly soluble drugs in water.
- For example, curcumin capsules in which the lipophilic or hydrophobic curcumin compound is encapsulated in whey protein microparticles enhances the solubility and bioavailability of curcumin's. The curcumin microparticles are further processed using a microfluidic jet-spray dryer to obtain uniform curcumin microparticles. When dissolved, the curcumin interacts with whey protein isolate (WPI) resulting in soluble complex formation through hydrophobic interaction which is directly proportional to concentration of WPI. It was found that nearly 100% of curcumin in the WPI microlayer was maintained in amorphous state and the WPI complexed microparticles can be easily rehydrated into a waxy dispersion independent to the temperature when they are dried at [12].
- Solid dispersions significantly enhance the dissolution rate, solubility, and bioavailability of hydrophobic drugs. The solid dispersions usually consist of two components: a drug that is usually hydrophobic and a hydrophilic matrix, which can either be amorphous or crystalline in form. Dispersion technology makes use of eutectic mixtures of water-soluble carriers with lipophilic drugs to improve their bioavailability. It has been estimated that about 40% of NCEs developed through combinatorial screening pose problems of solubility and are, therefore, difficult to formulate.
- The use of spray drying for preparing solid dispersions has been reported in a number of publications. Nilotinib, spironolactone, valsartan, and artemether are some drugs that have undergone solid dispersion to improve their solubility. [13-14].
- Soluplus was used as a carrier for the preparation of solid dispersions with nilotinib. According to the in vitro drug release studies, the best solubility of the drug was achieved at a drug-to-Soluplus ratio of 1:7, where it was shown that the drug solubility was improved by 630 times. In the study for dissolution of artemether solid dispersions, the Artemether to Soluplus ratio of level 1:3 was determined to be optimal, with the best formulation reaching approximately 82% release of the drug within one hour which was a 4.1 increase over the 20% release of the drug when it was devoid of any enhancements [15-17].
- The production of dry powder formulations, dry powder aerosols and thermo-labile materials has drying by spray as part of the process.
- With the use of spray dryer, there is a possibility to manufacture particles tailored in size, shape, and density for inhalation. Properties can be achieved and modified by changing the formulation composition and the process condition such as solvent system, the concentration of solute, atomization, feed rate, and the rate of gas into the dryer.
- Example: The TwinMax device for spray drying development of AP301 protein spray-dried powder showed that it is possible to produce stable dry powder inhalers with high doses of biopharmaceuticals while protecting their molecular bioactivity and ensuring proper aerodynamic properties.
- The aim of this study was to achieve greater efficiency for powder inhalation using lactoses or polyethylene glycol 6000, which were added as micronized powders (at 2.5%-10% w/w fine particle lactose) to the resulting blends of the powders with lactose monohydrate. The lactose monohydrate was a carrier for aerosol dry powders created through co-spray drying of maltodextrin and BSA and were relevant for inhalation use.
- Sucrose worked well as a protective agent when spray drying oxyhemoglobin and trypsinogen. Without sucrose, roughly half of the oxyhemoglobin was changed into methemoglobin which is not useful in the transport of oxygen. But, with methemoglobin conversion, when a protective agent of sucrose 0.25M was employed, it was reduced to 4%. [18-20].

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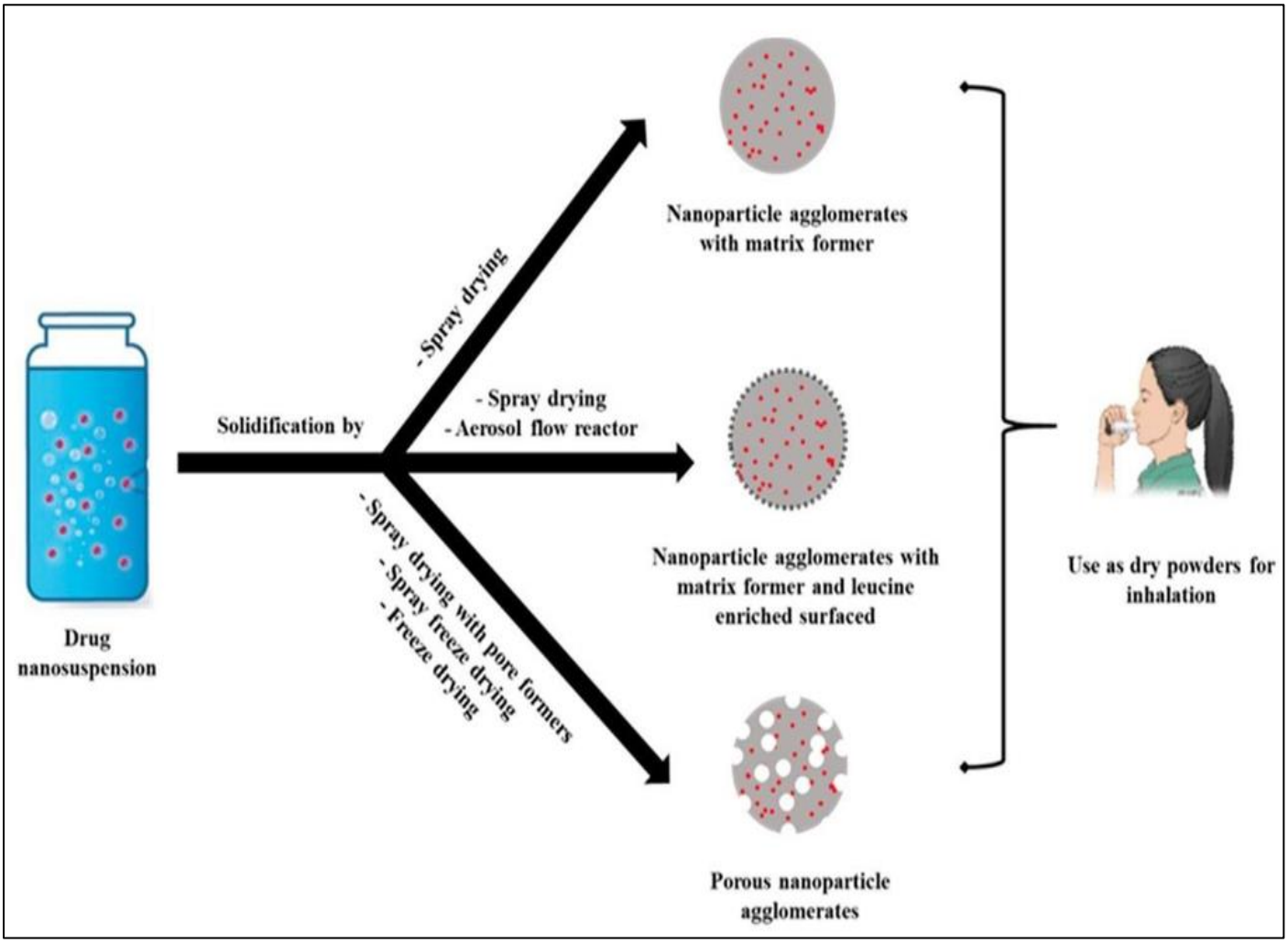

Fig 3 Dry Powder Inhaler Prepared by Spray Drier Technique.

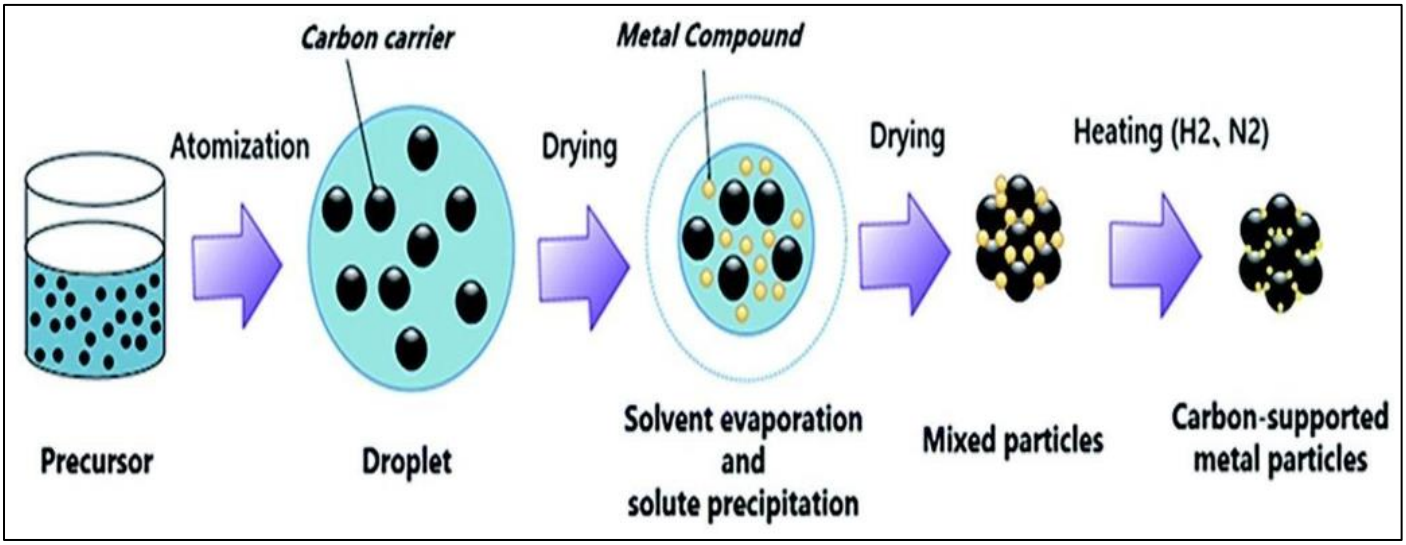

Fig 4 Prepare Innovative Nano-Particulate Formulations.

Next Generation Nano-Particulate Drug Products Prepared with Spray-Drying Technology. The field of pharmaceutical nanotechnology, especially the use of "nanomedicine," has significantly transformed drug delivery systems by further increasing the therapeutic value through maximizing bioavailability of the drug supplied. Controlling the release of hydrophilic and lipophilic drugs, polymeric nanoparticles with good physicochemical stability can be dried by spray-drying which is a more versatile method.[21-23]

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VIII. PARAMETERS EFFECTING SPRAY DRYING PROCESS

➢ *Properties of Feed Solution:*

- The spray solution's viscosity, surface tension, and density impact both droplet atomization and formation. Its chemical stability allows for the feed solution to be sustained without degrading in needed processes such as filtering. The composition determines the properties that the particles are defined with when they are dried.
- Properties of Excipients and Solvents: Excipients play a role in helping the product become more soluble and stabilize the final product. The choice of solvent impacts the development of the particles and drying efficiency.
- Feed Concentration/Preparation: Feed solution with a higher concentration generates low-density porous particles in the final product. A feed solution with a lower concentration yields greater particle density and smoothness.
- Feed Rate: A high feed rate will lead to a larger yield alongside a greater average moisture content in the end product. A low feed rate corresponds to a decrease in yield and an increase in the average droplet size.
- Inlet and Outlet Temperature: The inlet temperature controls the heat transfer, drying speed, and defined shape of the dry particle for the solution being processed. The outlet temperature controls the moisture in the end product.
- Drying Airflow/Atomization Process: Different dryer designs shape the atomizer nozzle which will alter the size of the atomization droplets and the efficiency of the drying process. The flow rate of the atomizing gas defines the particle formation and regulates the spray conditions.
- Gas Type: The use of nitrogen, air, or carbon dioxide dictate the level of crystallization as well as transfering heat to the particles for drying in granulation processes turning the liquids to solids. The use of a unidirectional flow changes the interaction the droplet has with the gas in defogging a cloud.

➢ *Process Optimization Techniques:*

- Design of Experiment (DoE): A methodical approach to look for important process factors.
- Computational Fluid Dynamics (CFD): Implemented across the board in predictive spray drying modeling.[24]

Table 1 Examples of Polymers used as Carrier for Preparing Spray-Dried Formulation [25]

Drug and rout of administration	carrier	Drug: carrier ratio (w/w)	Solvent	Process parameters	Yield (%)	Particle size	Particle morphology	Advantages
Carbamazepine for oral administration	Chitosan HPMC	1:1 7:3 9:1	for crude drug: ethanol 96% for samples loaded with HPMC: ethanol/water 2:3 (v/v) for samples loaded with chitosan: 0.5% acetic acid	inlet temperature: 120°C outlet temperature: 75°C spray flow rate: 0.25 L/h air flow rate: 700 N×L/h	~30	~3	Spherical micro-spheres	drug amorphization; faster drug release from chitosan-HPMC composite microparticles than those made of HPMC; sustained drug release possible
Andrographolide for oral administration	PVP	1:2 1:3 1:4	Methanol	inlet temperature: 60°C outlet temperature: 45°C feed rate: 6–8 mL/min	60–70	2.8–3.6	spherical micro-particles	micronization; drug amorphization; stabilizing effect of hydrogen bonds; 5-fold solubility increase

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				atomization air pressure: 2 kg/cm2				
Felodipine for oral administration	PVPVA	1:4	Acetone	inlet temperature: 72–184℃ outlet temperature: 32–61℃ feed rate: 110–188 g/min atomization air pressure: 2.11 kg/cm2 cyclone: 10.2 cm or 15.2 cm two-fluid nozzle or pressure swirl nozzle	66–90	4–115	intact, collapsed or fractured hollow spheres	drug amorphization; flowability of amorphous solid dispersions suitable for compaction; high mechanical resistance of tablets
Diltiazem for oral administration	Eudragit RS & Eudragit RL	1:2 1:4 1:8	DCM	inlet temperature: 70℃ outlet temperature: 57–60℃ feed rate: 2–5 mL/min spray-flow: 700 N×L/h 0.5 mm nozzle	N/A	1–9	smooth micro-spheres	narrow particle size distribution; drug amorphization; high drug load results in faster release rate

Table 2 List of Commonly used Solvents in Spray Drying Technology [26]

List of solvents	Boiling point (°C)	Dielectric constant	Solubility in water (g/100 g)	Density (g/ml)	ICH limit (ppm)
Acetone	56.2	20.7	Miscible	1.049	Class 3
Chloroform	61.7	4.81	0.795	1.498	60
Methanol	64.6	32.6	Miscible	0.791	3000
Methylene chloride	39.8	9.08	1.32	1.326	600
Ethanol	78.5	24.6	Miscible		Class 3
Dimethyl formamide	153	36.7	Miscible	0.944	880
Dimethyl sulfoxide	189	47	25.3	1.092	Class 3
Glycerin	290	42.5	Miscible	1.261	-
Ethyl acetate	77	6	8.7	0.895	Class 3
Water	100	78.54	-	0.998	-

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IX. CONCLUSION

Alongside the technological advancements occurring in the medical realm, spray drying is regarded as a major drug formulation technology due to its role in improving the solubility and bioavailability of poorly water soluble drugs. Not only is the technology scalable, but it is also feasible for a variety of formulations including controlled release drug formulations and nanoparticulate drug delivery systems. Overcoming flaws related to residual solvents, low flowability, and effectiveness through innovation and better material. The growing fields of pharmaceutical development as well as changing aspects of spray drying processes will lead to constant innovations which will overcome formulation problems, stability issues, and the need for new drug delivery systems.

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