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A Review on Spray Congealing: An Innovative Technology for Novel Drug Delivery Systems

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ABSTRACT:

Spray congealing is an economical and straightforward method for producing microparticles without relying on organic or aqueous solvents. This review comprehensively examines the pharmaceutical applications of this technology, focusing on spray-congealed drug delivery systems. It begins by outlining the fundamental principles and necessary equipment involved in spray congealing. Following this, notable examples of drug delivery systems are discussed critically, highlighting the impact of formulation variables and practical considerations in formulation design. The review also addresses the current industrial applications of spray congealing within the pharmaceutical sector. The latter sections detail the advantages and limitations of this technology, as well as its future potential in drug delivery systems. The method's capabilities in microencapsulation, taste-masking, and controlled release are compared to other commonly used technologies like spray drying and hot melt extrusion. Notably, the ability to control powder characteristics without the need for extensive downstream processing distinguishes spray congealing from other particle engineering methods. This review emphasizes the significance of spray congealing for enhancing solubility and bioavailability, exploring the mechanisms behind these improvements. Additionally, it provides insights into the key factors to consider during the manufacturing and characterization of spray-congealed solid microparticles. Challenges related to the poor solubility and bioavailability of both existing and newly synthesized drugs continue to hinder the development of environmentally friendly pharmaceutical formulations.

Keywords: Spray congealing, Spray chilling, Spray Prilling, Spray cooling, Microencapsulation Techniques, multiarticulate drug-delivery systems, solid dispersion, solid lipid microparticles, solvent-free technology.

Introduction:

Multiarticulate novel drug delivery systems (NDDS), particularly microparticles (MPs), have garnered significant interest over the past few decades. Unlike traditional single-unit dosage

forms, MPs distribute the drug across multiple discrete delivery entities. This approach offers several advantages, including improved dispersibility in the gastrointestinal (GI) tract, enhanced bioavailability, reduced risk of dose dumping and systemic toxicity, decreased dosing frequency, better patient compliance, and minimized variability in absorption. Additionally, their flexibility makes MPs particularly appealing for developing personalized pharmaceutical products. While traditional methods for producing MPs are well-documented, emerging techniques like spray congealing have received limited attention. Spray congealing is a cost-effective, straightforward, and environmentally friendly method that eliminates the need for solvents, making it suitable for various applications in food, nutraceuticals, and pharmaceuticals. There is a growing demand for effective drug delivery systems (DDS) that can control, localize, and improve drug release.

Microencapsulation is an expanding technology that involves applying thin coatings to small solid particles or liquid droplets. This process transforms liquids into solids, alters surface and colloidal properties, provides protection from environmental factors, and controls the release characteristics of the coated materials.

Various microencapsulation process is:

1) Air suspension

2) Coacervation-phase separation

3) Mult orifice centrifugal

4) Pan coating

5) Solvent evaporation

6) Spray drying

7) Spray congealing.

The increasing demand for innovative pharmaceutical formulations has heightened interest in spray congealing, a technique that combines aspects of spray drying and hot melt extrusion. This method not only accommodates many systems typically produced via these traditional techniques but also enables the creation of powders with unique properties for applications such as microencapsulation, taste masking, and controlled release. The primary focus of this paper is to provide an overview of the role of spray congealing in the pharmaceutical industry, assessing its advantages and disadvantages compared to more commonly used methods like spray drying and hot melt extrusion. Often referred to as spray chilling or spray cooling, spray congealing involves atomizing a liquid melt into a cooling chamber. During this process, molten droplets transition from a liquid to a solid state as heat is removed. The spray congealing procedure can be described in four key steps: (1) atomization of the melt into droplets, (2) interaction of the droplets with a cold congealing gas, (3) solidification of the droplets into particles, and (4) separation of the solidified particles from the cooling gas. A sufficiently cold gas, typically introduced in a co-current flow, contacts the droplets, facilitating solidification. A simplified diagram of the spray congealing process illustrates these steps.

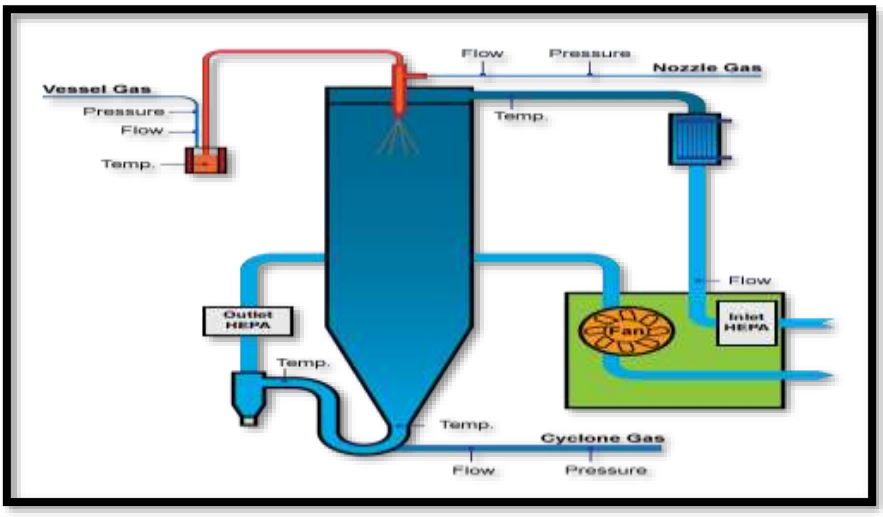

Figure 1: simplified scheme of the spray congealing.

Advantages:

- Uniform Particle Size
- High Purity
- Control Over Particle Morphology
- Flexibility
- Efficient
- Low cost
- High performance and reproducible physical process
- No need of organic solvents.

Spray congealing: principles, excipients & equipment:

Principles:

1. Atomization: Liquid feed is sprayed into small droplets.

2. Cooling: Droplets come into contact with a hot gas stream, causing rapid cooling.

3. Solidification: Droplets solidify into small, uniform particles.

4. Collection: Particles are collected and separated from the gas stream.

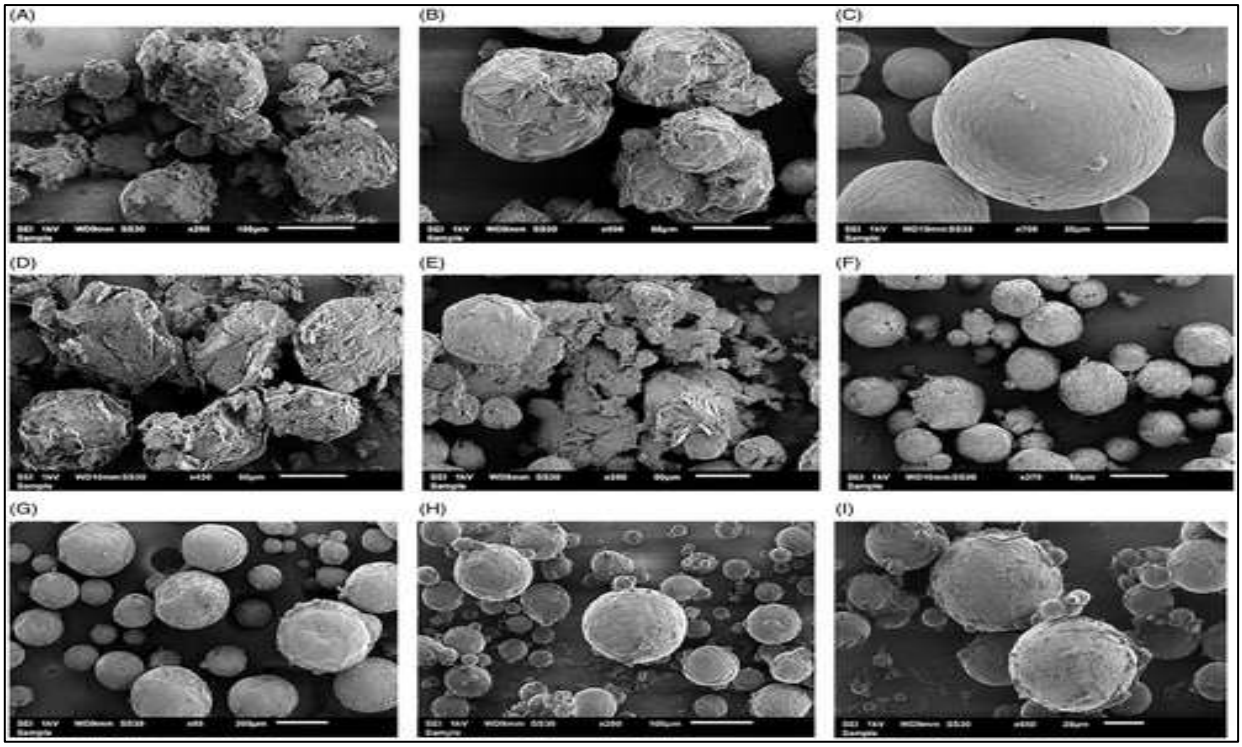

Figure 2. Scanning electron microscopy images of spray-congealed carnauba wax solid lipid microparticles

Excipients:

Common excipients used in spray congealing:

1. Fillers (e.g., lactose, starch)

2. Binders (e.g., cellulose, gum Arabic)

3. Lubricants (e.g., magnesium stearate)

4. Disintegrants (e.g., crospovidone)

5. Coatings (e.g., ethyl cellulose)

Equipment:

Key components of spray congealing equipment:

1. Spray Nozzle: Atomizes liquid feed.

2. Cooling Chamber: Hot gas stream cools droplets.

3. Cyclone Separator: Separates particles from gas stream.

4. Filter: Collects particles.

5. Heater: Controls temperature.

Types of spray congealing equipment:

1. Spray Dryers

2. Fluidized Bed Spray Congealers

3. Spray Congealing Towers

4. Centrifugal Spray Congealers

5. Ultrasonic Spray Congealers

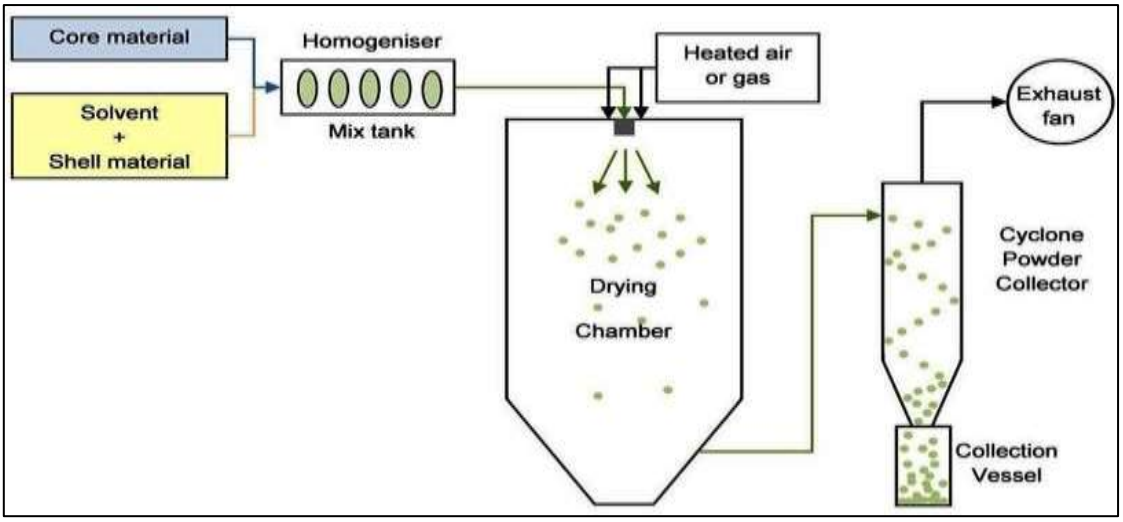

Figure 3: Scheme of the spray congealing technology and process stages.

Operating Parameters:

Critical parameters affecting spray congealing:

1. Temperature
2. Flow rate
3. Pressure
4. Nozzle design
5. Gas-to-liquid ratio

Spray congealing technology: General aspects

The core substance is mixed with a coating material solution, then atomized, and dried using heated gas in a drying chamber. Both spray drying and spray congealing are efficient, single-step processes suitable for large-scale production, whether in batches or continuously. Spray drying works for both thermolabile and thermostable substances, producing uniformly sized particles. In contrast, spray congealing does not require water or organic solvents, resulting in multiarticulate dosage forms. These forms consist of numerous small units, each containing a portion of the active pharmaceutical ingredient (API), offering advantages such as better dispersibility in the gastrointestinal tract, reduced risk of dose dumping, decreased systemic toxicity, lower dosing frequency, enhanced patient compliance, and consistent absorption. Additionally, their small size minimizes reliance on gastric emptying, reducing variability in gastrointestinal transit times, making them ideal for tailored pharmaceutical solutions.

Recently, spray congealing, also known as spray chilling or spray cooling, has gained popularity due to its simplicity and lower time and energy requirements compared to other methods. It enables the production of spherical, free-flowing microparticles that are ready for tableting or encapsulation without extensive post-processing steps, achieving high encapsulation efficiencies (90–100%). The spray drying process involves converting a liquid solution or suspension into a powdered solid by introducing it into a drying chamber, where it meets hot drying gas. The resulting wet gas and dry particles are separated, and the powder is collected. In contrast, spray congealing atomizes a fluid, typically a melted carrier solution with the drug, in a chamber kept below the carrier's melting point. The first step includes preparing the fluid by maintaining the molten carrier above its melting temperature along with the active ingredient.

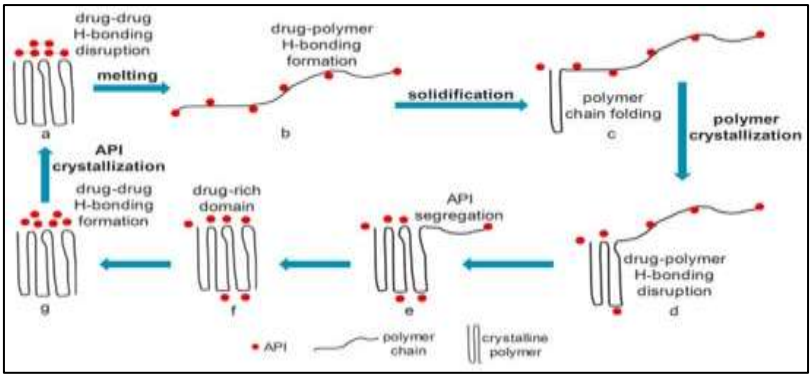

Figure 4: Scheme of a general spray congealing apparatus with the different steps for the production of microparticle.

The efficiency of the spray congealing process is heavily reliant on the atomization of the molten fluid. Therefore, the atomization phase is critical and can be executed using several types of atomizers, including pressure nozzles, two-fluid (pneumatic or air) nozzles, rotary nozzles, and ultrasonic nozzles. For those seeking in-depth information on the various equipment and nozzles used in spray congealing, a recent review offers a comprehensive discussion on these topics.

Structure and Composition of Spray Congealed SD:

The structure of spray-congealed solid dispersions (SDs) generally includes:

1. Matrix: This is the continuous phase, often made up of hydrophilic carriers such as polymers (e.g., PVP, PVA, HPMC), sugars (e.g., lactose, sucrose), or waxes.

2. Dispersed phase: This phase contains a hydrophobic active pharmaceutical ingredient (API), which may be molecularly dispersed or exist as micro- or nanoparticles within the matrix.

3. Interface: The boundary region between the matrix and the dispersed phase, which can significantly affect the physical and chemical stability of the SD.

The process of spray congealing poorly water-soluble APIs in these carriers can lead to the formation of solid dispersions with either crystalline or amorphous drug forms, or solid solutions where the drug is molecularly dispersed in the carrier. In many cases, especially at higher drug concentrations, a mixed state may occur when the drug exceeds its solubility in the carrier. This results in solid dispersions that can exhibit different physical states (crystalline, amorphous, or partially crystalline) based on the characteristics of both the drug and the carrier, their miscibility, and possible interactions.

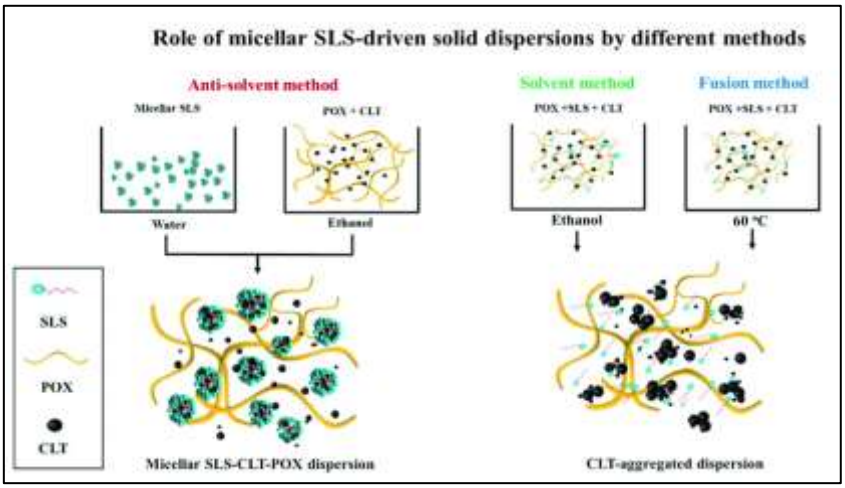

Figure 5. Scheme depicting the different type of solid dispersions that can be obtained by spray congealing (orange arrows represent individual API molecules).

Composition:

The composition of spray-congealed solid dispersions (SDs) typically comprises:

1. Active Pharmaceutical Ingredient (API): This hydrophobic drug can constitute 10-90% (w/w) of the total formulation.

2. Carrier: A hydrophilic carrier, which also accounts for 10-90% (w/w) of the composition.

3. Additives: Optional components like surfactants, anti-caking agents, or stabilizers to improve physical stability, flowability, or bioavailability.

Among the semicrystalline carriers, polyethylene glycol (PEG) is frequently utilized due to its low toxicity and affordability. PEG is a polymer of ethylene oxide with molecular weights that can range from 200 to several million g/mol. For SD formulations, solid PEGs with molecular weights between 1500 and 6000 g/mol are commonly used. PEG has a melting point of approximately 55 °C to 65 °C, depending on its molecular weight, and is often employed in melting-based processes. However, due to its very low glass transition temperatures (from −95 °C to −17 °C), stabilizing the amorphous form of PEG can be challenging, leading to crystallization of PEG during the preparation or storage of most PEG-based SDs.

Properties and Characterization of spray congealing:

A comprehensive evaluation of the properties of spray-congealed solid dispersions is essential, as these properties directly influence the technological and biopharmaceutical behaviour of the system. A schematic representation (Figure 6) illustrates the classification of relevant material properties and the methods employed for their analysis.

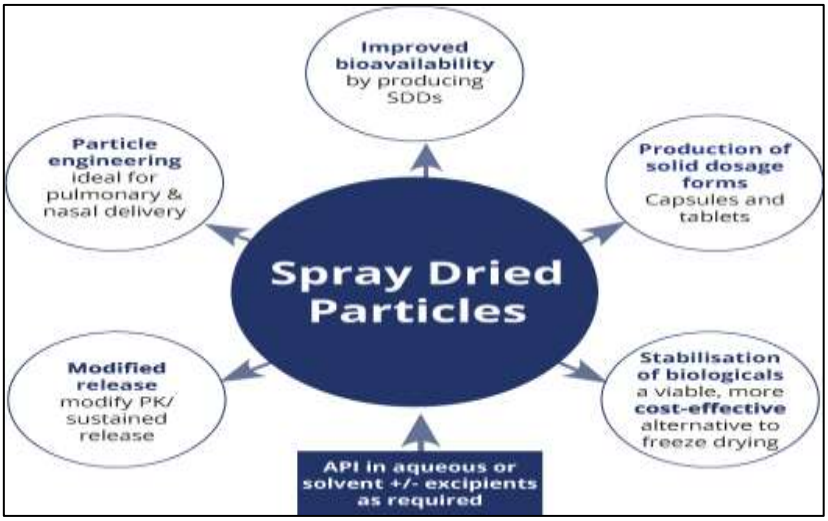

Figure 6. Schematic classification of the most commonly used techniques for the characterization of spray congealed SD.

1. Improved Solubility: The molecular dispersion of the hydrophobic API enhances its aqueous solubility.

2. Increased Dissolution Rate: Smaller particle sizes lead to faster dissolution rates due to a larger surface area.

3. Enhanced Bioavailability: Increased solubility and dissolution rates contribute to improved oral bioavailability.

4. Stability: Both physical and chemical stability are maintained due to the amorphous or crystalline nature of the formulation.

5. Particle Size: Typically, particle sizes range from 1 to 100 μm.

Particle size can be expressed as average diameter ± standard deviation or as median diameter (d50), indicating the size below which 50% of the sample lies by volume or mass. Additionally, d10 and d90 values represent the sizes below which 10% and 90% of the sample fall, respectively. The particle size distribution can also be reported to provide insights into the mono- or polydispersity of the material. Spray congealing commonly yields particles ranging from a few microns to hundreds of microns in diameter.

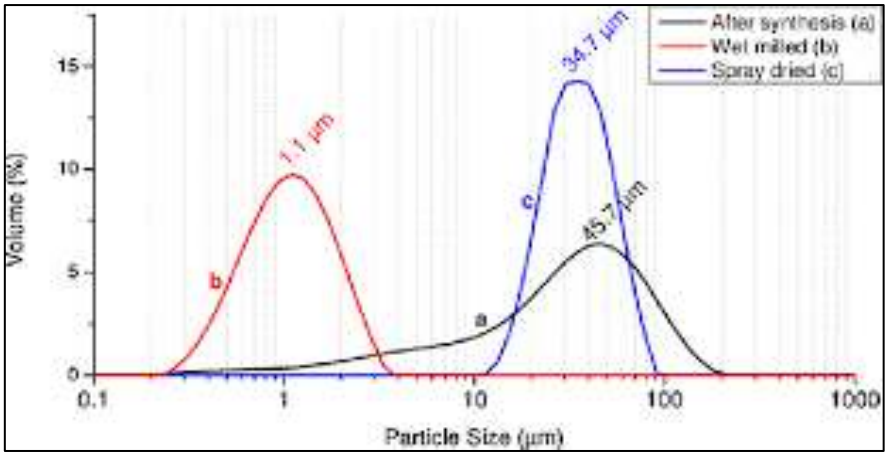

Figure 7. Particle Size

Examples of successful products:

Spray congealing has proven effective in encapsulating various pharmaceuticals within microparticles, including:

- Clarithromycin
- Theophylline
- Diclofenac
- Verapamil
- Indomethacin
- Propafenone hydrochloride
- Tocopheryl acetate
- Tetracycline hydrochloride
- Lidocaine hydrochloride

Notable Success Stories:

Pfizer's Zmax, an extended-release formulation of azithromycin, exemplifies the successful utilization of spray congealing technology in pharmaceutical development. This broad-spectrum antibiotic showcases the potential of spray congealing in creating effective, controlled-release medications.

Application of spray congealing:

1. Pharmaceutical (e.g., particle engineering)
2. Food (e.g., powder production)
3. Chemical (e.g., catalyst synthesis)
4. Biotechnology (e.g., encapsulation)

Industrial applications within the pharmaceutical field:

Despite the significant potential and academic interest in spray congealing for its reported benefits, its industrial applications in the pharmaceutical sector remain limited. Most patents in this area focus on veterinary medicine. Notably, one recent patent details an enhanced formulation of pimobendan, utilizing PEG 4000 or PEG 6000 microspheres. Another pertains to sustained-release injectable microspheres containing macrocyclic lactones.

Among patents aimed at human pharmaceuticals, a key example is the one by Appel et al., which introduces a spray-congeal method using an extruder to create multiparticulate azithromycin formulations that include a poloxamer and a glyceride. The inventors assert that their approach, which combines a twin-screw extruder with a spinning-disk atomizer, addresses limitations of previous melt-congeal methods by allowing for the production of molten droplets that congeal into multiparticulates.

Additionally, a recent patent application by Faure et al. describes a process for preparing an intermediate powder formulation and a final dosage form through a spray congealing step. This innovation incorporates at least one liquid component, such as vitamin E, within low melting point materials, enhancing the formulation's effectiveness.

Conclusions:

Spray congealing is a particle-engineering technique that enables the creation of formulations for microencapsulation, taste masking, and controlled release. Currently, its market presence is limited by the availability of equipment, scales, and expertise, particularly among Contract Research and Manufacturing Organizations (CRMOs). However, growth in this field is bolstered by the fact that the technology is an adaptation of spray drying, which is increasingly utilized to create amorphous solid dispersions that improve the bioavailability of poorly soluble drugs. One of the key advantages of spray congealing is the ability to control powder characteristics—such as particle size, morphology, and density—without requiring additional downstream processes like secondary drying, granulation, milling, or palletisation. Recent in vitro studies have confirmed its efficacy.

The spray congealing system, particularly when equipped with the novel WPN nozzle, can effectively nebulize highly viscous formulations that conventional equipment struggles to handle. Drug loading in microspheres can be significant, reaching 50% for propafenone hydrochloride and 30% for α-tocopheryl acetate, with yields nearing 95%. The particle distribution is relatively narrow, and drug release profiles can be tailored based on the lipophilicity or hydrophilicity of the excipients used.

This system presents a versatile and cost-effective manufacturing option, characterized by lower energy consumption and reduced processing time. Consequently, spray congealing shows substantial promise for producing microparticulate dosage forms in the pharmaceutical industry.

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