Conrad Winters

# Spray congealing: applications in the Pharmaceutical Industry

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KEYWORDS

Spray congealing; taste masking; controlled release; microencapsulation; particle-engineering.

ABSTRACT

In this work, the potential of spray congealing in microencapsulation, taste masking and controlled release was explored and compared to other commonly used technologies, specifically spray drying and hot melt extrusion. The ability to control powder characteristics without the need of subsequent downstream processing methods is a marked advantage over other "particle-engineering" technologies. Moreover, spray congealing is an environmentally friendly process where high throughputs can be achieved. This technology involves some critical stages that should be thoroughly evaluated when establishing the process, namely the atomization, cooling and feed stages. Spray congealing represents a very attractive and promising platform to address some of the challenges related to drug development and drug life cycle management.

## INTRODUCTION

The increasing demand for new formulations as part of drug life cycle management or to address New Chemical Entities challenges is boosting the use of spray congealing, which can be described as a combination of spray drying and hot melt extrusion techniques. This platform can match many of the systems prepared by spray drying or hot melt extrusion but also enables the preparation of powders with unique properties and applications in microencapsulation, taste masking and controlled release. The main goal of this paper is to provide an overview on the applications of spray congealing in the pharmaceutical industry and compare this technology, presenting the advantages and drawbacks, with others more commonly used like spray drying and hot melt extrusion.

Spray congealing, also called spray chilling or spray cooling, is a unit operation in which a liquid melt is atomized in to a cooling chamber. A sufficiently cold gas stream enters the chamber, typically in co-current configuration, i.e. flowing in the same direction, contacting the droplets and solidification takes place. This involves the transformation of molten droplets from liquid to solid state with removal of energy from the droplets. The transition of a melt from a soft or fluid state to a rigid or solid state by cooling is called congealing. Hence, the spray congealing process can be described by four events: i) atomization of the melt into droplets , ii) contact of the droplets with the cold congealing gas, iii) solidification of the droplets into particles and iv) separation of the particles from the congealing gas. A simplified scheme of the spray congealing process is shown in Figure 1.

The platform is gaining attention driven by the generation of high performance materials and short processing times. Compared to other "particle engineering" technologies like spray drying, process times are often shorter because solvents are not used and post-processing is typically not required. Spray drying typically produces hollow, low density particles with irregular geometry, whereas spray congealing, with its lack of evaporative solvent effects, is able to produce spherical and dense microparticles suitable for tableting, capsule filling or injection. With appropriate polymer selection, these dense microspheres can provide for diffusion-controlled or erosion-controlled drug release.

Drug particles are typically dissolved, suspended or entrapped in a molten matrix. The matrix can be of

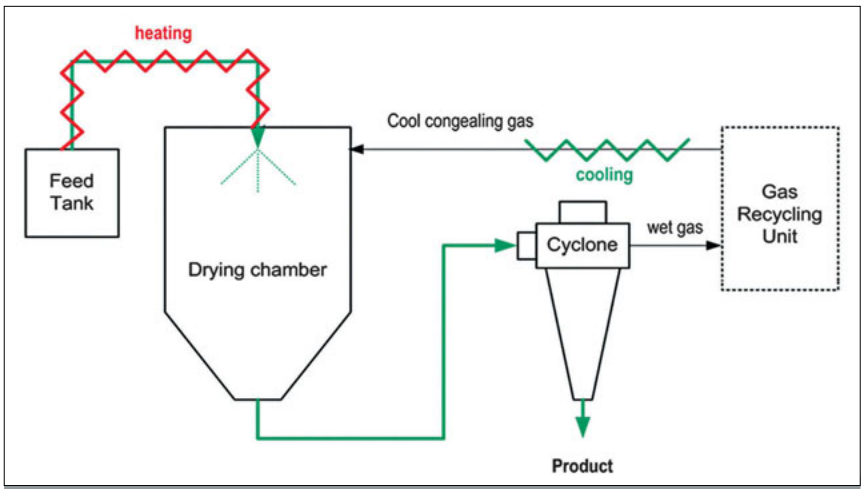


*Figure 1. Standard spray congealing setup.*

hydrophilic or hydrophobic low melting point carriers, and the resultant slurry is pumped into the spray congealing unit. The selection of a suitable carrier can mask the taste of bitter drugs or be used to modify their dissolution behavior. The operating conditions may also impact the properties of the final product. There have been a number of works reported in the literature where spray congealing was assessed. Savolainen *et al.* (1) prepared controlled release tablets of a poorly soluble drug where spray congealing was used to formulate the drug and excipients into a solid dispersion which was then compressed. Changes in the physical properties of the drug such as particle size and crystallinity enabled the change of the drug release rate. Passerini *et al.* (2) evaluated the suitability of spray congealing as a technique for enhancing the dissolution rate of a low water soluble drug. Microparticles with different drug loadings were prepared with success and a higher drug dissolution rate was observed for all the microparticles when compared to the dissolution rate of the pure active ingredient and without changes of its solid state. Moreover, this study also contemplated the examination of the microparticles shape and surface characteristics, and microparticles with a drug load higher than 10% revealed small acicular structures on their surface, suggesting that an efficient drug coating was not completely achieved for higher drug contents.
Maschke *et al.* (3) developed a spray congealing process for the preparation of insulin-loaded microparticles, where the impact of operating conditions, namely atomization pressure and spraying temperature, on particle size and process yield was studied. Spray congealing was proved to be an excellent platform to produce protein-loaded microparticles, taking full advantage of lipids as an alternative material for the controlled release of proteins. The choice of the appropriate matrix is a point of paramount importance in the control of the drug release profile since it impacts both the erosion rate and hydrophobicity. Usually, materials with a low HLB (Hydrophilic-Lipophilic Balance) value, i.e., with lipophilic characteristics, are the preferred choice for controlled release purposes. Passerini *et al*. (4) showed that through the appropriate selection of the type and amount of carriers, microparticles having a spherical shape, good encapsulation efficiency and a zero-order release for 8 hours in a pH 1.2 buffered solution, can be obtained without modifying the solid state properties of the drug.
Taste masking is fundamental for the successful development of solid oral dosage forms as it correlates with patient compliance. Many drugs have a bitter or unpleasant taste and spray congealing can be used with success for taste masking purposes. This is particularly important in the development of pediatric dosage forms. In this case, the selection of the optimal drug / excipient ratio, as well as the process temperatures, are key for the taste masking efficiency. In addition, other operating conditions like nozzle wheel speed and feed flow rate were also shown by Yajima *et al.* (5) to have influence in the taste masking efficiency, being the congealing speed of melt droplets the dominant factor in masking the bitter taste of the drug. A high atomizer wheel speed, for manufacturing a small matrix, and an optimum liquid feed rate, for manufacturing a spherical matrix with a smooth surface, provided excellent operating conditions for taste masking.

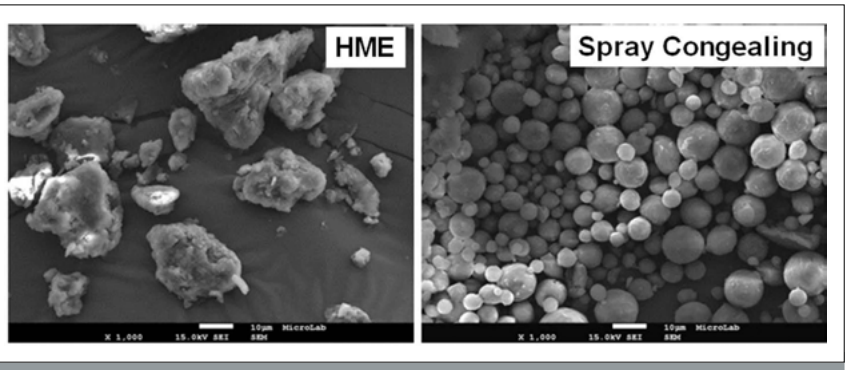


*Figure 2. Scanning electron microscopy images of materials produced by two distinct taste masking processes: hot melt extrusion (HME) and spray congealing (SC).*

## SPRAY CONGEALING VS TRADITIONAL TECHNOLOGIES

Spray congealing is a hybrid technology between spray drying and hot melt extrusion, accordingly sharing advantages and disadvantages of both technologies.
Spray drying consists in feeding a liquid stream (solution, suspension or emulsion) into a drying chamber where it is continuously divided into very fine droplets by a process known as atomization. A hot gas enters the chamber and drying of the droplets takes place. In summary, the core substance is dispersed in a solution of coating material, which is then atomized and the solvent dried-off using heated gas in a drying chamber. Both spray drying and spray congealing have the main advantage of being rapid and single-step operations, suitable for batch or continuous production of large quantities of product. Spray drying is suitable for both thermolabile and thermostable materials and enables the production of uniform size particles. The main advantage of spray congealing when compared to spray drying is that particles are prepared without the use of an aqueous phase or organic solvents. This is an environmentally friendly process, with associated economic benefit, that is particularly attractive for processing moisture-sensitive drugs. High throughputs are achievable and hence this technology is less time and energy consuming than spray drying. Microspheres are typically ready-to-use without further need of post-processing (e.g. secondary drying, granulation, milling, pelletization).
Hot melt extrusion (HME) is a process that can be run as batch or in continuous mode that is used as an effective means to mask the bitter taste of some drugs (6, 7) and also to control the drug release profile (8-10). HME is a cost-effective technology, very robust and easy to scale-up but has some drawbacks when compared to spray congealing. The main disadvantage, especially if the purpose is to mask the taste of the drug, is related to the downstream processing of HME that by necessity includes the milling or pelletization of extrudates. This downstream processing increases the probability of having drug molecules at the particle surface. Moreover, particles are not as smooth-surfaced as the ones obtained by spray congealing. The previous is observed in Figure 2 where microparticles of a model drug were microencapsulated in the same excipient with 40% API load using these two technologies. In the materials prepared by hot melt extrusion, the roughness observed is indicative of drug crystals at the surface while in the powders produced by spray congealing spherical materials with controlled morphology/particle size were obtained. In addition to taste characterization, the drug content on the surface of the microparticles can also be assessed by analytical tools such as Scanning Electron Microscopy (SEM) or X-ray Photoelectron Spectroscopy (XPS) analysis.

Albertini *et al.* (11) evaluated the release profile of solid lipid microparticles containing high amounts of a sunscreen agent. Microparticles with a sunscreen agent loading between 40.1 and 48.5% were prepared by spray congealing or a traditional melt dispersion method, aiming to have an efficient modulation drug release from the solid lipid microparticles. Spray congealing was shown to be preferable over the traditional melt dispersion method given the better release modulation and the photoprotective efficacy of the microparticles obtained by spray congealing. These observations can be partially explained by the higher coating efficiency of this latter technique that allows a better drug entrapment within the microparticle. The melt dispersion method, combined with the high drug load, led to the accumulation of the sunscreen agent on the microparticles surface promoting a faster drug release.

Spray congealing represents a proven technology for the formulation of drug-loaded microparticles with good encapsulation efficiency and a good control over particle size, by controlling the operating conditions. Spray congealing is a very attractive technology for the formulation of temperature and moisture sensitive materials.

| Pressure | Two-fluid | Rotary | Ultrasonic |
|---|---|---|---|
| - Not feasible for high viscosity melts, very high pressures are generated<br>- Acceptable particle size distribution<br>- Variations in nozzle design are being developed to allow higher viscosity feeds (e.g. wide-pressure nozzle) | - Allows broad range of melt viscosities and drug concentrations<br>- Wider particle size distribution<br>- Requires long congealing chambers | - Allows broad range of melt viscosities and drug concentrations<br>- Good particle size distribution<br>- Particle size dependent on rotation rate<br>- Requires large-diameter congealing chambers | - Allows broad range of melt viscosities and drug concentrations<br>- Good particle size distribution<br>- Good encapsulation efficiency |

*Table 1. Comparison for the different types of nozzle used in spray congealing processes.*

## CRITICAL PROCESS PARAMETERS

Spray congealing involves some critical stages that should be thoroughly evaluated when establishing the process. The most critical stages in the formation of spray-congealed particles are the atomization and the cooling but the feed stage can also play an important role in the overall process.

### *Feed stage*

The feeding system should be properly thermo-regulated to avoid both hot spots that could induce degradation and cold spots that could lead to setup blockage. Additionally, a change in the temperature of the feeding system may change the viscosity of the feeding melt and thus impact the properties of the final product.

The impact of short and long-term exposure to a high temperature, typically above the matrix melting temperature, should be carefully evaluated. The evaluation of the crystalline / amorphous nature of the drug can be undertaken by Differential Scanning Calorimetry (DSC) analysis and the level of impurities at different time points can be evaluated by High Performance Liquid Chromatography (HPLC). This information can help in the selection of the feed setup and the excipients. There are a few rules of thumb for the definition of the melting conditions:

1) Temperature of the melt should be 10°C above the melting temperature of the excipient(s). Adjustments might be necessary depending on the drug degradation profile;
2) It is recommended to work with a feed viscosity lower than 500 mPas. Higher viscosities may be possible but only with appropriate nozzle design;
3) Drug loads for microencapsulation are usually limited to 50%.

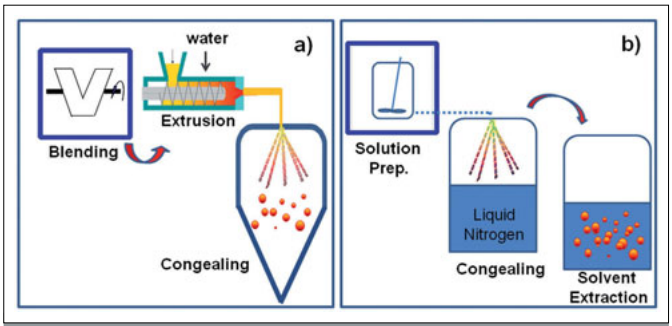


*Figure 3. Spray congealing setup: a) combining the feed with and hot melt extrusion process (used in Zmax®) and b) spray congealing with cryogenic solvent extraction (used with Nutropin Depot®).*

### *Atomization stage*

The nozzles or atomizers used in spray congealing processes should be able to handle high viscosity mixtures at high temperatures. Four types of nozzles may be used: pressure, two-fluid, rotary and ultrasonic nozzles. The selection of the type of nozzle is mainly dependent on the final product specification needs, with rotary and two-fluid nozzles being the most commonly used. Table 1 shows a comparison for these different types of nozzle.

### *Congealing stage*

Chamber dimensions are nozzle-dependent, but different chamber designs can be used to confer product advantages:

- Co-current and/or counter-current gas flow rate;
- Injection of solid fines to decrease cooling requirements;
- Fluidized mode to increase residence time and improve powder properties;
- Open-chamber concepts are also used.

A few rules of thumb should be taken into consideration when establishing the congealing conditions:

- Assure that at least 1/3 of the particle is solidified before contact with the wall to avoid sticking and disintegration. Larger particles require a longer residence time;
- Time for solidification is dependent on:
  1. Particle velocity;
  2. Particle size;
  3. The specific heat capacity of the material;
  4. Temperature and flow rate of the cooling gas;
- Cooling rate can impact the polymorphic form of the carrier and/or drug obtained;
- The inlet temperature of the cooling gas may go from -10°C to room temperature and is product and setup dependent.

### *Examples of successful products*

Spray congealing has been successfully used to prepare microparticles loaded with drugs such as clarithomycin (5), theophylline (12), diclofenac (13), verapamil (4),

indomethacin (14), propafenone hydrochloride, tocopheryl acetate (15), tetracycline hydrochloride and lidocaine hydrochloride (16), among others. Zmax®, Pfizer's extended release administration of azithromycin (a successful broad spectrum antibiotic), is a good example of a successful spray congealing product. The immediate release drug product (Zithromax®) has been available in the United States since 1992. Zmax® was approved as a one-dose-only treatment for mild-to-moderate acute bacterial sinusitis (ABS) and community-acquired pneumonia (CAP) in adults. With this new formulation, it became possible to complete the therapy in a single two-gram dose and increase the drug content in the target tissue by three fold compared to the standard dose of immediate release azithromycin (17, 18). Moreover, treatments were reduced from 7-14 days to 1-5 days with comparable efficacy.

| Product | Technology | Company | Phase |
|---|---|---|---|
| **Zmax ®** (azithromycin dihydrate) | Bend Melt-Spray-Congeal Microspheres | Pfizer | Marketed |
| **Nutropin Depot ®** (somatropin) | Alkermes ProLease ® | Genentech | Marketed Discontinued |
| **Prolease r-hFSH** (follitropin) | Alkermes ProLease ® | Merck Serono | Phase 1 Discontinued |
| **Procrit Prolease** (erythropoietin alpha, recombinant human) | Alkermes ProLease ® | Janssen | Pre-Clinical Discontinued |

*Table 2. Examples of spray congealing market / discontinued products.* *Source: PharmaCircle*

Zmax® microspheres (typically between 50 and 300 micron) are produced using a modified spray congealing apparatus (Figure 3a) (19). The process involves blending (azithromycin dihydrate, glyceryl behenate and poloxomer 407), forming a molten mixture / suspension of the drug in the carrier using an extruder, followed by atomization and congealing to form the microspheres.

Spray Congealing is also a suitable platform for the microencapsulation of thermo labile compounds, particularly proteins and peptides. In ProLease®, the modified spray congealing process developed by Alkermes (Figure 3b), the drug is dissolved / dispersed in a polymer solution in organic solvent (e.g. PLGA - poly(lactic-co-glycolic acid - in dicloromethane) and then atomized into liquid non-solvent for polymer (e.g. liquid nitrogen or antisolvent mixtures with ethanol) at a temperature below the freezing point of the polymer / drug solution, freezing the polymer / drug droplets. As droplets and non-solvent are warmed, the solvent in the droplets thaws and is extracted into the non-solvent, resulting in hardened microspheres. Due to the inexistence of a water-oil interface and continuous use of low temperatures, the potential denaturation of proteins is reduced, making it suitable to microencapsulate large molecules (20).

Examples of development / market programs with large molecules are provided in Table 2. Nutropin Depot®, Genentech's somatotropin drug product, is a good example of a peptide / hormone processed with ProLease® platform. The product approved by the Food and Drug Administration (FDA) in 1999 for the treatment of growth hormone deficiency in children, and discontinued because it required significantly more resources to produce than the rest of the Nutropin line, enabled an extended release profile with 2 or 4 weeks administrations. Other examples of large molecules that used Alkermes platform are Prolease r-hFSH, discontinued sustained release formulation (Alkermes / Merck Serono) of recombinant human follicle stimulating hormone (r-hFSH) for the treatment of infertility, and Procrit Prolease, a recombinant human erythropoietin to control red blood cells production.

## FUTURE PERSPECTIVES

Spray congealing is a "particle-engineering" technology that enables the preparation of formulations with applications in microencapsulation, taste masking and controlled release. The market is still limited to the number of equipments, scales and expertise available (Contract Research and Manufacturing organizations) but growth is supported by the fact that the apparatus is an adaptation of spray dryers, a technology expanding in use due to the need for amorphous solid dispersions to improve the bioavailability of poorly soluble drugs. The ability to control powder characteristics (particle size, morphology, density) without the need of other downstream processing methods (e.g. secondary drying, granulation, milling, pelletization) is a marked advantage over other methods.

Drawbacks of the technology are often related to the challenges of operating at high temperatures and high viscosities. Work in this field is increasing and the literature reveals examples of novel material use, as the incorporation of plasticization agents (e.g. polyethylene glycol, carbon dioxide) or alternative apparatus designs (e.g. combining HME screws with the spray congealing feeding / atomization system).

Spray congealing represents a very attractive and promising platform to address some of the challenges related to drug life cycle management and development of certain New Chemical Entities, with expected growth in the number of approved products using this platform in the next few years.

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