Excipient enhanced growth (EEG): Expanding delivery options for the treatment of lung diseases

Formulation and design approaches for excipient enhanced growth

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Abstract

In the treatment of lung disease, a novel pathway known as excipient enhanced growth is progressing through toxicological studies and showing promise for the treatment of both asthma and lung cancer by delivering active molecules to target sites in the lungs. The following article expounds on the formulation development process for two candidates, budesonide and gemcitabine, for local lung delivery using this formulation approach in combination with traditional spray drying for the generation of respirable engineered particles.

Background

Local treatment of lung diseases by the inhalation route is a therapeutic area with increased interest following the COVID-19 pandemic, although platforms for delivery to the lung have been common for centuries. Today, respiratory delivery, by either metered dose inhaler (MDI) or dry powder inhaler (DPI), is standard-of-care for numerous diseases, such as chronic obstructive pulmonary disease (COPD) and asthma. In recent years, local delivery has been investigated in clinical trials for additional lung indications such as pulmonary hypertension, lung infections and lung cancer. The reduced risk of systemic adverse effects and the potential for reduced dose are compelling advantages of local delivery.

Lung cancer continues to have a poor prognosis in most patients, which can be attributed to the ineffective delivery of drugs to the lung tissue with standard therapies. Inhaled delivery of pharmaceuticals is an approach that circumvents the shortcomings of standard intravenous (IV) delivery, including trypanophobia and hospital visits. Prior attempts at lung delivery have had issues either reaching the lungs or with treatment exhalation after initial delivery. However, an innovative excipient enhanced growth (EEG) platform for inhalation drug delivery offers a mechanism to overcome previous issues and has high feasibility for transporting a promising therapeutic agent directly into the lungs.

Originally developed at Virginia Commonwealth University (VCU), the technology is now being commercialized by Quench Medical, Inc., which has partnered with Lonza AG, for the spray drying of two compounds to utilize the platform and further demonstrated its efficacy. The two compounds, budesonide and gemcitabine, are intended to treat asthma and non-small-cell lung cancer, respectively. Budesonide is precedented for lung delivery to treat asthma, but gemcitabine is limited to intravenous dosing. Both Quench Medical EEG programs are currently in toxicological studies and show promise.

Rat studies, including lung histology, conducted by Quench Medical at Lovelace Biomedical Research Institute using this technique to deliver gemcitabine via inhalation to lung cancer tumors resulted in a significant decrease in lung weight and in the prevalence of tumors. Figure 1 shows the lung weight results from the study while Figure 2 shows a qualitative decrease in tumor prevalence [1]. Figure 1

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and Figure 2 together paint an effective picture of the benefits of direct lung delivery compared to standard-of-care IV treatment.

This article focuses on the formulation development and selection of Quench Medical EEG dry powder formulations in the development of two clinical treatments for lung diseases. Budesonide will be used to treat local lung inflammation and gemcitabine will be dosed for the treatment of non-small-cell lung cancer. EEG allows for highly targeted drug delivery into the lungs and can be robustly manufactured via a spray-drying particle engineering method. This dry powder inhalation platform can be flexibly scaled according to manufacturers' needs and may be appealing for a variety of inhalation-based therapies.

Excipient enhanced growth formulation: An overview

The EEG formulation platform results in a three-component engineered particle with the active pharmaceutical ingredient as one obvious component. The remaining two excipients are functional, including a surface modifier and a hygroscopic agent. The surface modifier of choice is often leucine, which migrates to the surface of particles and is used to enhance the dispersion of powder during inhalation. The hygroscopic component acts to draw water into the particles, increasing their size and resulting in deposition of even the finest particles [2]. Their contribution makes it necessary to include a high fraction of ultrafine particles, <1 µm, to allow for deep lung delivery. The hygroscopic agents explored in subsequent sections are sodium chloride and mannitol.

Generation of the ultrafine composite particles can be achieved by spray drying. The three components are dissolved in a common spray solvent system at up to 2% solids. Spray drying is often most successful from high volatility organic systems. However, for lung delivery, aqueous-based systems are often preferred to minimize the amount of residual solvents delivered to the lung. For the two programs, water or water/ethanol blends are used to appropriately solubilize the drugs and excipients.

The solution is then fed into the spray dryer via a two-fluid atomizer, where the appropriate droplet size is formed and subsequently dried using a heated drying gas stream [3]. Each of the formulations discussed below was spray dried on a customized spray dryer with a total gas flow of 35 kg/hr with solutions flow rates and outlet temperatures appropriate to achieve a thermodynamic balance and adequate drying conditions. The target particle size distribution is centered around 1.5 µm, resulting in particles which allow for deposition across the lung when combined with the size increase afforded by the combination of the hygroscopic agent and the high humidity environment of the lung. This is an intentional strategy to drive a high percent deposition in the deep lung. The Hindle/Longest Labs at VCU demonstrated a difference in deposition of a similar formulation on a Next Generation Impactor (NGI) at low and high humidity [4].

Due to the functional relationship with humidity, relative humidity at the outlet of the dryer becomes a key control parameter during manufacture. Similarly, controls must be taken with respect to packaging and handling during testing. If laboratories are prone to medium-to-high ambient humidities, a controlled environmental chamber may be necessary for any characterization.

Figure 1

Efficacy of inhaled EEG gemcitabine formulation with matched dose and half-dose vs IV standard-of-care. Reprinted with permission [1].

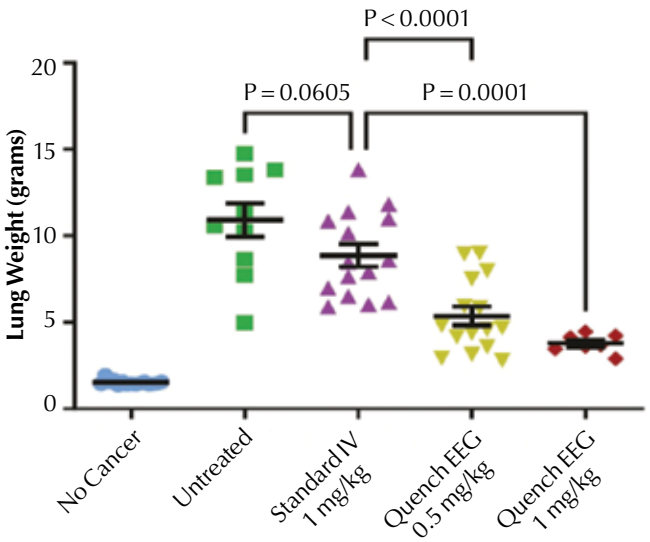
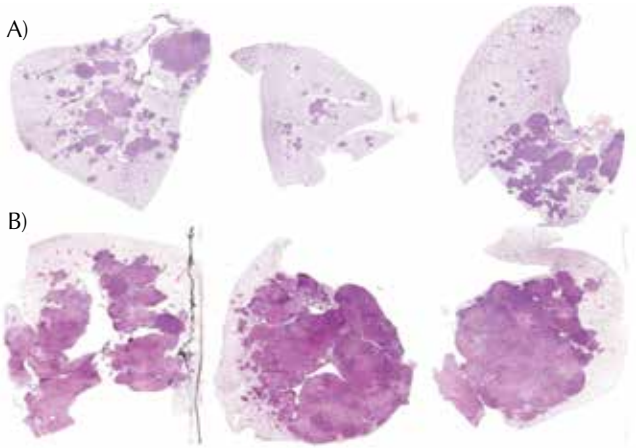


Figure 2

Tumor burden via histology of cancerous lesions in purple with (A) inhaled EEG gemcitabine formulations (0.5 mg/kg) and (B) standard-of-care IV gemcitabine (1 mg/kg). Reprinted with permission [1].



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Budesonide formulation selection

For the budesonide/lung inflammation program, the formulation selection journey began with two-fold technical assessments. The first was the assessment of solubility in blended water/ethanol systems as the active ingredient has low aqueous solubility and the excipients of choice such as sodium chloride, mannitol, and leucine have good solubility in water. The solubility data informed the operating space and enabled a total solids loading of 1% in a 50/50 ethanol/water solvent blend.

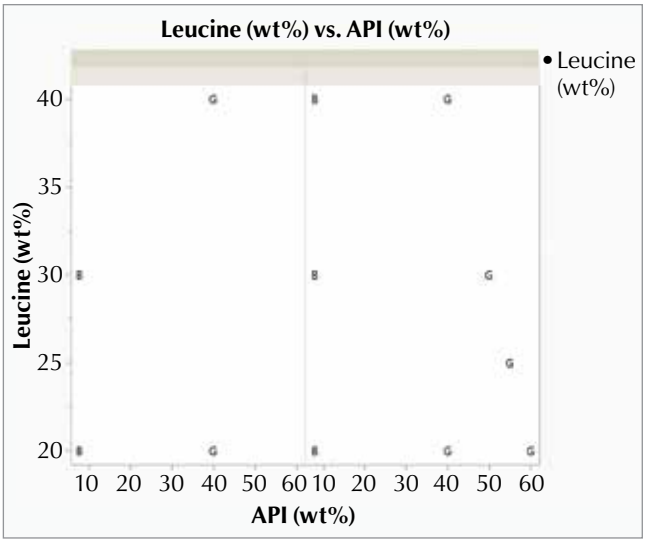
The second assessment included process space probing to generate and collect the correct particle sizes from the spray dryer. As mentioned above, these formulations necessitate a smaller particle size compared to those normally considered for inhalation. In spray drying, the particle size is determined by the droplet size formed during atomization and the solids content of the solution being sprayed. The droplet size is a function of the ratio of liquid to gas flow rates at the nozzle.

In the budesonide case, the target particle size distribution would have a Dv50 of 1.5 µm or less compared with more standard inhalation delivery formulations which target a Dv50 of around 2.5 µm. For reference, the Dv50 is a common particle size distribution metric by which 50% of the distribution on a volume basis is less than the metric and 50% is larger than the metric.

Initial spray conditions were refined on the feasibility scale dryer through three sprays of 3 grams each.

Figure 3

EEG formulation design space showing concentration of active pharmaceutical ingredient and leucine in test formulations for both programs. B indicates budesonide formulations and G indicates gemcitabine formulations.



Processing conditions were altered to increase yields, decrease particle sizes and decrease outlet humidity conditions. An 8/72/20% budesonide/mannitol/leucine model formulation was chosen for this work, and would later be the basis around which the formulation composition is explored.

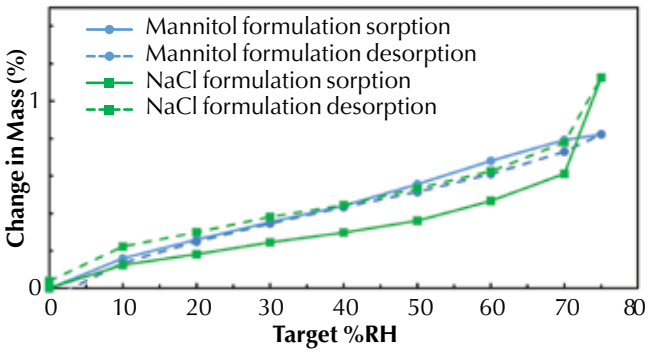
With improved processing conditions, five EEG formulations were carried into the study and manufactured using the same equipment setup (Figure 3). The formulation space included both hygroscopic components, sodium chloride and mannitol, as well as an assessment of leucine loading. Literature data suggests that 10-20% leucine is all that is needed for sufficient dispersion enhancement [5]. However, both mannitol and sodium chloride could compete for the surface so higher amounts of leucine were deemed interesting for this study. Higher amounts of leucine also allow the critical concentration threshold to be reached earlier in the drying process, which improves stability performance.

An initial round of characterization was performed to assess the chemical and physical properties of each formulation. Assay, geometric particle size, water content, residual solvent, morphology, crystallinity and thermal properties were performed on all formulations. Water sorption and desorption were performed on both the mannitol and sodium chloride formulations with 72% of each hygroscopic EEG component for comparison (Figure 4). Sodium chloride demonstrated a slightly higher amount of water uptake than mannitol, making it a potentially preferred excipient over its mannitol counterpart.

Considerations for moving forward with two formulations included: manufacturability (specifically yield and difficulty/time/cost) and desired physical and chemical properties. The 8/62/30% mannitol and sodium chloride formulations were further progressed, testing their stability after one month at 25 °C/60% relative humidity (RH) and 40 °C/75% RH stored

Figure 4

Water sorption/desorption curves for leading formulations. Comparisons between formulations with mannitol and sodium chloride are shown.



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in mylar bags with desiccant. Geometric particle size, water content, crystallinity and thermal properties showed minimal change from the initial timepoint for both conditions, demonstrating stability of both spray-dried intermediates. Considering the formulation design, both water content and particle size changes on stability are of high concern.

Ultimately, the leading formulation contained 8 wt% budesonide, 30 wt% leucine and the remainder sodium chloride based on water uptake during dynamic vapor sorption testing and favorable short-term stability performance.

Successful one-month stability allowed the program to move forward with scale-up feasibility work on a clinical-scale dryer. Processing conditions were optimized for spraying 8/62/30% budesonide/sodium chloride/leucine (Bud/NaCl/Leu) and targeting particles with a Dv50 of approximately 1.3 microns. Overall, analytical characterization of four different processing conditions showed relatively little difference between each spray lot except for geometric particle size. As expected, sprays with lower particle size distributions were more difficult to collect, resulting in a lower yield. Further optimization was made, including tradeoffs between geometric particle size and yield, which ultimately led to successfully manufacturing the leading formulation at a clinically relevant scale for both toxicological supplies and long-term stability assessment.

Gemcitabine formulation selection

Building upon the foundation from the budesonide EEG formulation feasibility, a gemcitabine formulation study was initiated. In this case, IV dosing indicated a high API loading was necessary, along with the hygroscopic excipient and surface modifier. Active pharmaceutical ingredient loading was probed from 40% to 60% and leucine content was varied from 20% to 30%. The remaining formulation space was filled with sodium chloride. A single formulation containing mannitol was formulated as a comparator to sodium chloride performance (Figure 2). The optimized spray-drying process from the previous studies was leveraged for this work on the feasibility-scale dryer.

Initial characterization of these formulations consisted of the following tests: water content by Karl Fischer titration, assay/related substances by high performance liquid chromatography (HPLC), particle morphology by scanning electron microscopy (SEM), thermal characterization by modulated differential scanning calorimetry, appearance, physical state by X-ray powder diffraction, particle size distribution by Malvern Mastersizer (Malvern Panalytical, Malvern, UK) and water sorption by dynamic vapor sorption. The water sorption profile was of particular interest for understanding the operating space and thresholds for these hygroscopic formulations. A crystallization event was identified above 40% RH for both the sodium chloride and mannitol formulations. A form change from amorphous to crystalline can have adverse effects on desirable aerodynamic properties. Considering this data, along with the hygroscopic nature of the formulation, the handling and packaging of these powders was critical. To further understand the formulation space and performance, all formulations were staged onto stability with approximately 0.5 g in a glass amber vial overpackaged in a mylar bag with desiccant. Samples were placed in environmental chambers held at 25 °C/60% RH and 40 °C/75% RH. Performance and stability feasibility were large drivers for the success of this formulation platform.

The one-month stability results were critical in formulation selection. The sodium chloride formulations showed minimal change after one month at both conditions. The mannitol formulation exhibited some increase in particle size growth at the accelerated condition, most notable under the Dv90 measurement by Malvern Mastersizer. Interestingly, the mannitol formulation had the lowest water content after one month on stability. This would suggest the mechanism for particle growth was likely not driven by the hygroscopic formulation design. Leveraging the initial formulation characterization, the particle morphology of the mannitol formulation did appear slightly smoother than its sodium chloride counterpart at equivalent leucine loadings. It is hypothesized that, in this system, perhaps there is poorer leucine surface enrichment for the mannitol formulation as a result of mannitol competition for the surface. With less leucine on the surface, this could lead to a difference in surface energy with the potential for particle growth or agglomeration over time on stability. Furthermore, this was illustrated visually by scanning electron microscope at the one-month timepoint, demonstrating crystalline growth occurred. (Figures 5 and 6.)

Along with repeating the same testing panel as the initial timepoint, aerosol properties were determined using a Fast Screening Impactor (FSI) (MSP, a Division of TSI, Shorewood, MN, US) with a 5-micron cutoff plate. Introducing the FSI screening was a useful tool in deciphering among the formulations after one month to quantify aerosol behavior after stability and rank order formulations. Only the accelerated condition (40 °C/75% RH)was tested, to better gauge impacts of stability. This screening test, shown in Figure 7, highlighted the preference for 40/40/20%, 50/20/30% and 55/20/25% gemcitanibe/sodium chloride/leucine, based on aerosol performance after one month at 40 °C/75% RH.

Considering the impact of stability on geometric particle size, not surprisingly, the mannitol formulation was outperformed by the sodium chloride aerosol properties. The aerodynamic properties of

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Figure 5

Representative particle morphology captured by SEM for the sodium chloride formulation 40/40/20% Gem/NaCl/Leu.

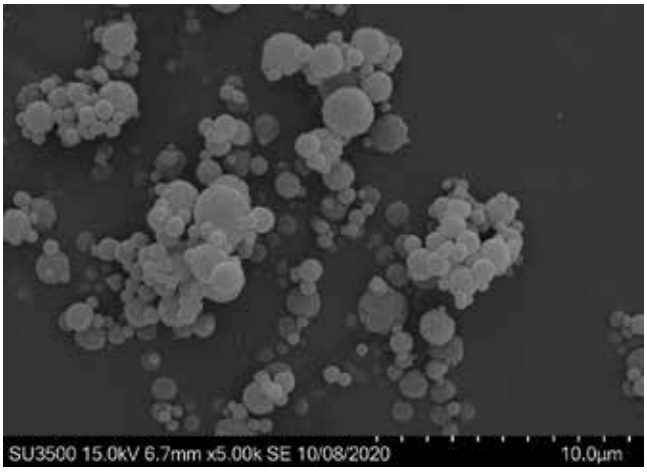
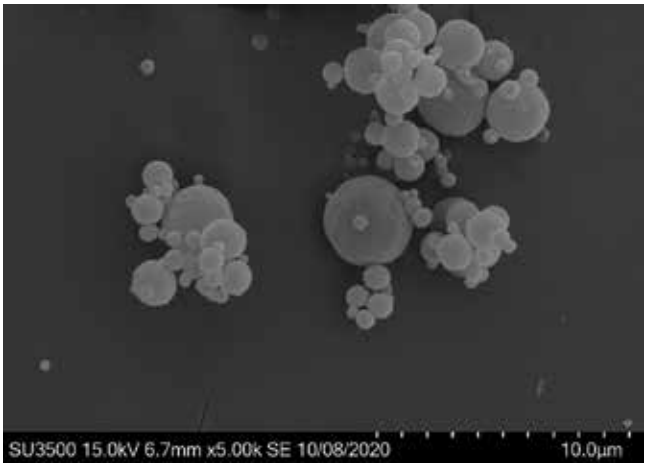


Figure 6

Representative particle morphology captured by SEM for the mannitol formulation 40/40/20% Gem/Mann/Leu.



the 50/20/30% gemcitabine/sodium chloride/leucine (Gem/NaCl/Leu) formulation were among the best of all five formulations. This formulation also was among the highest in terms of yield and physical stability characteristics. This formulation became the leading candidate, and was progressed through the remaining stability study, along with a backup sodium chloride formulation.

Conclusions

The excipient enhanced growth (EEG) formulation strategy is a breakthrough technology that has the potential to meet the long-elusive need for delivering medications directly into lung tissue without complications from first-pass metabolism, blood-volume dilution or systemic effects. There are currently two programs seeking to advance this technology through toxicology studies sponsored by Quench Medical: budesonide for the treatment of asthma and gemcitabine for local treatment of non-small-cell lung cancer. In conjunction with Lonza, there has been a robust study of formulation and particle design, culminating in short-term stability and scale-up to clinically relevant scales.

Although the two programs utilize a similar formulation design and manufacturing process, each faced unique challenges. In the case of budesonide, manufacturability was the challenge. There was more emphasis in the gemcitabine program on stability results. In both cases, mannitol and sodium chloride were studied for their performance as a hygroscopic agent and different leucine levels were compared.

In the comparison of hygroscopic excipients, sodium chloride had more favorable performance with both budesonide and gemcitabine. The decision in the budesonide case was based around the water sorption benefit of high amounts of sodium chloride while the decision for gemcitabine was focused on stability results. This may be due to the higher drug load of the formulation.

Both programs resulted in a similar leucine loading of 30 wt%, which allowed for good dispersion and stability performance. This is in the center of the range studied, suggesting a local optimum. Future work for these programs includes manufacturing robustness and potential clinical supplies.

Along with the potential for improving lung cancer survival rates, EEG therapies offer the potential for greater efficacy in treating a broad range of lung diseases while reducing side effects. The EEG formulations may well be the logical leap in drug delivery necessary to open new markets for previously unfeasible or ineffective therapies.

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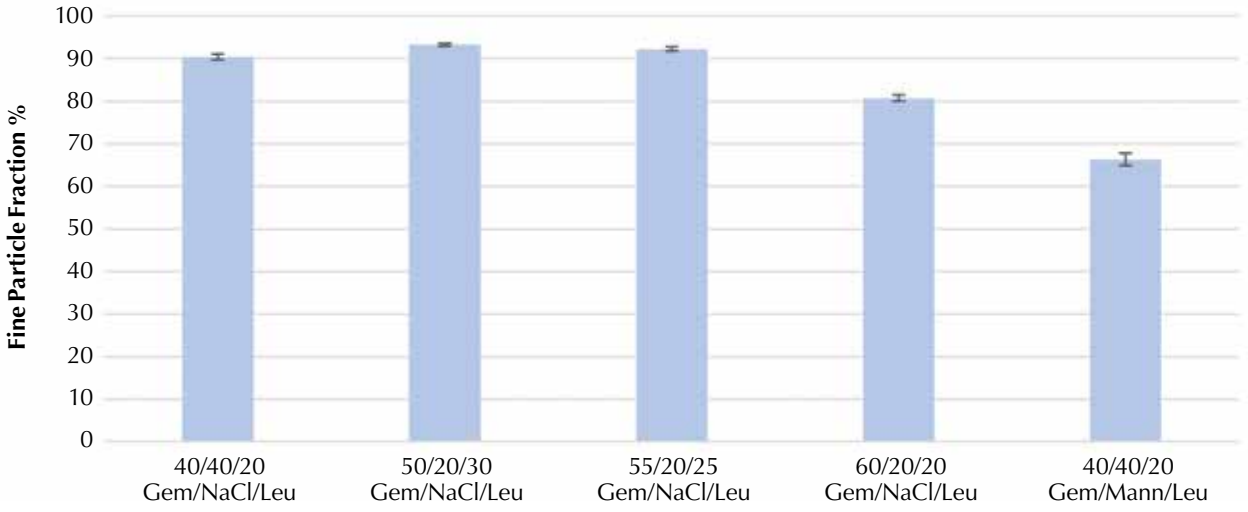
Figure 7

Gemcitabine formulation comparison after 1 month, via fine particle fraction captured by FSI screening. Standard deviations are shown in black and indicate good agreement between samples.



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