INTERNATIONAL JOURNAL OF PHARMACEUTICAL EXCIPIENTS

A message from the Editor

Keith Horspool, Chief Editor*

This issue of the IJPE highlights the continued innovation in excipients. Later in the issue, there is a report from Sarkar et al, that continues the recent focus on exploring the potential of alternative natural sources of excipients. The first article of this issue is dedicated to a series of overviews recounting the exemplary research conducted by recipients of IPEC Foundation's Graduate Student Award, and summaries of winners of the Patrick DeLuca Emerging Researcher Award which recognizes a beginning career scientist (post Ph.D.) who has demonstrated interest and dedication to the area of excipients. This award provides financial support for research for up to two years. Khanh Tran was the recipient of the award this year, and Sichen Song was recognized for his award that was granted in 2024.

Please note that two distinguished scientists were also recognized with 2025 Foundation Awards: Paul Heng (National university of Singapore) received the Ralph Shangraw Memorial Award that recognizes individuals who have provided outstanding research contributions in the study of excipients or excipient-related technology; Örn Almarsson (AXELYF) was honored with the Henk de Jong Industrial Research Award that recognizes individuals working in an industrial setting who have made significant contributions in the field of excipient technology. (Note: summaries of presentations made by these two award winners are not provided in the article.)

It is exciting to learn of emerging scientific insights, new experimental methods, and new technologies/techniques that represent step-changes to how excipients can be utilized in ever-expanding ways, using ever-expanding approaches, for facile development of both NCE and NBE formulations, with common goals to reduce empiricism by increased (molecular) understanding and to increase the confidence in formulation design and development. Greater knowledge of underlying processes, and critical factors, influencing the technical probability of success have enormous potential to drastically reduce the speed of development and, most critically, to enable products to be made available to patients more quickly. Importantly, several of the presentations reported ways to apply computational and AI-based tools that offer extremely powerful opportunities for informed decision-making in development of more complex systems, especially those that contain more challenging therapeutics such as peptides, mRNAs, vaccines, etc.

The following article provides a précis of each award-winning research project. These summaries have been generated, *in absentia*, from material presented during the event. Brief personal perspectives on the impact of each project have been added at the end of each summary.

*Corresponding author
125krh@gmail.com

For additional information on the various IPEC Foundation's annual awards please refer to a summary in last year's IJPE December issue and the official website for the IPEC Foundation. Note that this site also contains information relevant for any graduate scientists wishing to apply for an award next year.

As this is the final issue of the IJPE this year, on behalf of IPEC-Americas and myself, I would like to thank all authors for submitting their manuscripts to the IJPE, and for their help in preparing the final published articles. I would also like to recognize members of the Scientific Review Boards, and Editorial Board, for their outstanding support and commitment to the journal.

With very best wishes for the holiday season and for a wonderful 2026.

Excerpts from the IPEC Foundation's annual awards ceremony

San Antonio, November 11, 2025

Keith Horspool

Understanding Effects of Hydrophobic Amino Acids on Hygroscopic Spray Dried Powders for Inhalation on Aerosol Performance, Dissolution, and Cellular Uptake

Yijing Huang, Purdue University

Spray dried formulations for dry powder inhalers (DPIs) are often vulnerable to moisture-induced deterioration of aerosol performance. This research work evaluated the ability of hydrophobic excipients to mitigate this challenge and thereby preserve aerosol performance. DPI formulations were produced by spray drying the active, colistin, alone and in combination with either leucine or trileucine. Aerosol performance was determined using the next-generation impactor (NGI) with samples of recently prepared powders and samples that had been stored at 75% RH for one week. Particle morphology was assessed using scanning electron microscopy (SEM) and surface element analysis was conducted using X-ray photoelectron spectroscopy (XPS). The crystallinity of colistin in native and stored samples, in the presence of the hydrophobic excipients vs drug alone, was evaluated using X-ray diffraction (XRD). Furthermore, dissolution and cellular uptake + transport studies using the H441 epithelium model (Franz cell) were used as surrogates for assessing drug efficacy and safety.

Trileucine and leucine were able to increase the moisture resistance of spray dried colistin and to rejuvenate its aerosol performance, with values approaching that determined prior to storage of colistin at 75% RH for one week. Both excipients decreased the surface concentration of the drug in the SD particles. Improved resistance to moisture-induced deterioration of aerosol performance by trileucine was attributed to its better surface enrichment efficiency compared to leucine. The difference in surface enrichment did not result in any differences between the two excipients in powder dissolution or cellular uptake. Small particle size and incomplete surface coverage were considered likely reasons for the excipients performing similarly in these two studies.

This research addresses the fundamental challenge of moisture-induced deterioration of aerosol performance of spray dried DPI formulations stored at high humidity. Hydrophobic excipients provide interesting opportunities for creating more stable and robust formulations that maintain their delivery performance and safety and represent valuable materials for enabling DPI products for the future.

Impact of Polyethylene Glycol Polymer in the Development of Long-Acting Injectable Suspensions

Nileshkumar Malavia, University of Connecticut

Long-acting injectable products are highly desirable for several therapeutic applications (e.g., oncology, CNS disorders) to improve the effectiveness of therapy by ensuring compliance through sustained delivery achieved over weeks or months depending on the formulation composition. PEG polymers are commonly used in these formulations to modify the rate and extent of drug release during the treatment period. Variations in the molecular composition of manufactured PEG supplies therefore have the potential to affect drug delivery. This research work described methods to determine how differences in particle-polymer interactions could affect drug release profiles *in vitro* and *in vivo*, and the implications of such differences on performance.

Long-acting suspension formulations typically comprise of a poorly soluble, hydrophobic, drug (in micro or nanocrystalline form) combined with a stabilized surfactant and polymer system (such as PEG and polylactic acid co-glycolide, PLGA, respectively). The primary particle size of the drug controls the rate of release and the product duration; the extent of dissolution being described by the Noyes-Whitney equation with smaller particles having more rapid dissolution. In addition, suspension depots can also be influenced by the dispersing agent, such as PEG. This research program explored how differences in PEG composition could affect particle-polymer interactions resulting in potentially different agglomeration behavior.

Samples of PEG 3350 sourced from Spectrum Chemicals and BASF were characterized by thermogravimetric analysis (TGA), molecular fraction analysis, and molecular weight analysis. This polymer was used to prepare five nanosuspension formulations, designed to be Q1Q2 equivalent to Depo Provera 150® (which contains 150mg of medroxyprogesterone acetate, MPA). The five formulations varied according to the polymer source (FA and FC), or size of the MPA (FB 25m, and FD, FE 5m each). Subsequently these formulations were compared using *in vitro* and *in vivo* testing. Particle size determination was conducted using a Malvern Mastersizer, *in vitro* drug release studies were conducted using a modified USP type IV method. *In vivo* performance was assessed by measuring PEG 3350 levels in depots removed 14 days post intramuscular injection in New Zealand white rabbits, and by examining local toleration of the depot (that was determined using histopathology and immunohistochemistry analysis.)

Data from TGA showed that BASF PEG 3350 had a broad derivative peak compared to the material from Spectrum Chemical. The interpretation being that there was greater heterogeneity in the BASF PEG likely caused by variations in chain length, or due to the presence of residual monomers. Apparent differences between the PEG supplies were substantiated by gas permeation chromatography (GPC) that gave different values for the average molecular weight of the two materials: 3558 for Spectrum Chemicals, 3113 for BASF PEG 3350.

Particle size testing revealed that formulation FC was more shear sensitive compared to formulation FA. The particle size for FC was reduced by ~33% when suspension samples were syringed into the sizing well versus using a pipette for sample transfer. Formulation FA did not show any difference in size with the two different sample transfer methods. These results aligned with findings from *in vitro* drug release studies that showed faster initial drug release for FC versus that from formulation FA.

In vivo testing of the five different nanosuspensions showed differences in the amount of PEG 3350 retained at the depot site 14 days after administration. Formulations FA and FC had 95% and 78% retained at the site indicative of good particle polymer association. Formulations FD and FE had relatively low retention of 15% and 20% respectively, postulated to be due to particle-particle interactions outweighing particle-polymer interactions despite smaller particle size. There was very low residual polymer reported for formulation FB (5%) which was largely attributed to the larger particle size of this system. These differences were also somewhat reflected in the local responses at the depot site with histological analysis showing a hydrated gel-like matrix that was thought to slow the immune response by reducing cell migration to the site

and thereby containing the inflammatory response. Formulations FD and FE demonstrated limited cell infiltration. In comparison, the FB formulation, with its larger particle size, showed inflammatory cell presence both at the surface and within the depot.

This work highlighted reasons why PEG polymers are critical attributes in the development and supply of LAI depot suspension formulations. Different commercial supplies of PEG 3350 showed variations in their molecular composition, with potential implications on particle-polymer interactions, that were reported to cause subtle differences in the *in vitro* release profile of prototype formulations. Particle characteristics were shown to have effects on polymer retention at the depot injection site which were important in determining the morphology of the depot locally with consequent effects on the extent of local inflammation.

This is a valuable addition to scientific research aimed at increasing the understanding of complex formulations and how to determine how equivalent they are.

Understanding the Stabilization Potential of Polymeric Excipients for Spray-Dried Monoclonal Antibody Formulations

Chanakya D. Patil, Purdue University

Spray drying is an attractive alternative to freeze drying for manufacture of biologics because SD offers benefits in terms of its scalability and amenability to continuous manufacture. The challenge with SD is the risk of protein destabilization from both thermal and interfacial stresses encountered by materials during processing. Formulations typically contain stabilizers such as trehalose/mannitol to mitigate these risks but themselves have issues such as crystallization or formation of heterogeneous matrices during product storage that can reduce their effectiveness. This research program was designed to identify excipients with the potential to overcome these limitations while maintaining the protein structure, and functionality, in the solid state of an undisclosed monoclonal antibody (mAb). The primary focus was on evaluation of various polymers including hydrolyzed gelatin, 2-(hydroxypropyl)-β-cyclodextrin (HPCD), sodium carboxymethylcellulose (NaCMC), dextran (20kD), and polyvinyl pyrrolidone (PVP) K90 and K30. Performance of these materials was compared to the conventional stabilizers: trehalose and mannitol.

Spray dried (SD) samples were prepared by processing a liquid formulation based on a 1:1 protein:stabilizer ratio. These materials were stored at 40°C for 3 months followed by powder characterization, protein stability analysis, and investigation of excipient-matrix interactions.

All SD samples had a similar particle size of ~2.5μ and contained between 3-4% residual moisture. Results from size exclusion chromatography (SEC) analysis of the mAb highlighted the superiority of hydrolyzed gelatin as a stabilizer. Data for this excipient showed the lowest % monomer loss of the mAb (<5%) demonstrating that it preserved protein integrity during spray drying and through storage of the manufactured particles at elevated temperatures. Trehalose performed reasonably well, as expected, and its performance was matched by HPCD that had the added benefit of reducing interfacial stresses. Protein stabilization by PVP was dependent on its molecular weight with reasonable stabilization at higher molecular weight (K90) but poor performance with lower molecular weight material (K30) that gave evidence of phase separation. All other excipients were ineffective as stabilizers, especially mannitol that showed very deleterious behavior involving crystallization and consequent protein destabilization.

This work nicely demonstrates that effective stabilization of mAb formulations requires a sound understanding of the compatibility of the specific protein with the specific polymeric excipient stabilizers being considered for product design. The homogeneity of the protein-polymer matrix, and surface protein expsoure on the SD particles, dictated the solid-state stability

Can Molecular Descriptors Drive Nanosuspension Innovation? Leveraging Machine Learning and AI to Predict the Particle Size

Vishvesh Raje, St. John's University

This research aimed to shift formulation development from trial-and-error approaches toward predictive, data-driven design. Using three model excipient systems: HPMC-SLS (system 1), Kollidon K17 Tween 80 (system2), Albumin-Tween 80 (system 3), studies were conducted to determine which descriptors/molecular properties were important in predicting whether nanoparticles would fall into the categories of low (L), medium (M) and high (H) particle size or precipitated (P).

The objective was to develop robust machine learning models by evaluating multiple algorithms (Random Forest, SVM, Gradient Boosting, and XGBoost) to achieve optimal prediction accuracy for ~40 drugs formulated as nanoparticles using the three excipient systems. The nanosuspensions were processed by wet media milling using a Delta Vital Mill (NETZSCH) operated at 1500rpm. Subsequent particle size analysis of the nanoparticles was achieved using dynamic light scattering (DLS), with a Malvern Zetasizer Nano ZS. The frequency distribution of particle size, polydispersibility index (PI), and median particle diameter (D_{50}) was used as the basis for classifying the three nanoparticle systems into L, M, H, or P categories that were used for subsequent predictive modeling. In total, 38 drugs (and two formulations), along with 113 final descriptors (physical properties, surface interactions, chemical features), were used to generate target values of D_{50} for the three excipient systems.

Learning curves from initial training and cross-validation gave differences in F1 score across the various models. These findings highlighted the risks of a limited data set, resulting in generalizations with suboptimal accuracy. This was overcome to a significant extent through subsequent hyperparameter fine-tuning for example, a 25% improvement in the Gradient Boosting F1 determination for the HPMC-SLS formulation, ~ 70% improvement for the SVM value for the Kollidon-Tween 80 formulation, and for Random Forest, a 16.9% improvement for the Albumin-Tween 80 formulation.

Class distributions (% belonging to each distinct class or category) showed varying particle size outcomes for the three formulation systems, with the highest precipitation rate (42%) being reported for the Albumin-Tween 80 formulation.

Feature importance ratings showed formulation-specific molecular drivers: excipient systems F1 and F2 relied on a custom calculated property of Size Prediction Factor (smaller size tended to correlate with lower MW, moderate Log P, and higher TPSA). F3 was governed by stability indices (H-bond acceptor density, HLB-Estimated). PEOE_VSA6 was shown to be a common predictor across all formulations, characterizing the features of a molecule based on the combination of atomic partial charges and molecular surface area information.

The outcomes of this work highlighted how improved nanoparticle compositions were successfully designed using molecular descriptors, achieving F1 scores of 0.56-0.60 across three different excipient systems. While the scores demonstrated some room for improvement, this approach showed immense potential for formulation design based on molecular insights. Researchers stated that this is the first systematic experimental dataset analysis designed to determine the molecular drivers of nanoparticle behavior.

Nanoparticle systems are far more complex than the conventional powder formulations, and this study demonstrates the increased value of a more scientific approach which offers significant potential to eliminate empirical approaches that are extremely time-consuming and inefficient.

Mechanisms of Punch Sticking Induced by a Lubricant: Hydrogenated Vegetable Oil

Tianyi Xiang, University of Minnesota

Tablet manufacture can sometimes be compromised due to issues with sticking of material to punches that can result in tablet defects, and if necessary, manufacturing excursions as punches are cleaned of residual material. Lubricants can be incorporated in formulations pre-predisposed to sticking issues. Several lubricant excipients are available including hydrogenated vegetable oil (HVO). Rather surprisingly, this work showed that HVO, rather than circumventing issues, can induce sticking when incorporated in certain formulations. Potential mechanisms for this phenomenon were elucidated using prototype formulations of acetaminophen (APAP) with 2% HVO added internally. Sticking propensity was determined by plotting punch weight after single compression at various pressures and at 40 MPa with repeated compression. UV-Visible analysis was used to determine the amount of APAP extracted from the adhered mass (using ethanol). It was shown that the proportion of APAP in the material adhered to punches was similar to that in the original formulations, indicating that there are both excipients and APAP present in the adhered mass.

Tabletability analyses (pure HVO, pure APAP, 50% HVO + 50% APAP, 50% APAP + 50% excipient matrix) were used to characterize forces between particles: HVO-HVO (F_{HH}), APAP-APAP (F_{AA}), APAP-excipient matrix (F_{EA}). To assess the magnitude of the force between HVO and the excipient matrix (F_{HE}) relative to the force between HVO and the punch (F_{PH}), mixtures of 50% HVO + 50% excipient matrix) were compressed using a punch with a removable tip coated in a layer of HVO.

Plots of compaction pressure (MPa) versus tensile strength (MPa) demonstrated the following rank order of tabletability: that of pure HVO equivalent to 50% HVO + 50% APAP which was greater than pure APAP ($F_{HH} \sim F_{HA} >> F_{AA}$) and that 50% HVO + 50% excipient matrix was greater than 50% APAP + 50% excipient matrix ($F_{HE} > H_{EA}$). Furthermore, there was a constant amount of sticking after compression of pure HVO, irrespective of the applied pressure showing $F_{PH} > F_{HH}$. Using a punch coated with a layer of HVO there were positive weight increases across all compression pressures for a blend of 50% HVO + 50% excipient mixture indicating a greater magnitude of force between HVO and the punch than for HVO and the excipient matrix ($F_{PH} > F_{HE}$).

In summary, punch sticking behavior promoted by HVO is caused by the stronger adhesion of this excipient to punch surfaces compared to punch adhesion of APAP and other excipients. HVO then can cause neighboring APAP particles to stick to the punch because $F_{PH} > F_{HA} > F_{AA}$. Alternatively, an HVO particle on the punch surface can induce adhesion of neighboring excipients and APAP particles because $F_{PH} > F_{HE} > F_{EA}$.

This compaction force-based model shows great potential as a mechanistic approach to investigate other examples of lubrication-induced sticking.

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Artificial Intelligent-Guided Excipient Screening for Vaccines and Therapeutic Delivery Systems

Khanh Tran, Massachusetts Institute of Technology.

Many of the most promising therapeutic modalities in recent years have required relatively sophisticated formulations that have multiple components, some of which can be novel or relatively new excipients. The opportunity to develop effective delivery systems to enable optimal delivery of these medical breakthroughs brings with it the challenge of an enormous design space, with relatively low prior knowledge to enable effective development paradigms that increase the technical probability of success and reduce the speed of development. In this work microneedles were the specific focus based on their ability to address some of the challenges to vaccine drug delivery, namely the reliance on cold chain storage and the requirement for trained personnel to train patients in product administration. Specifically, dissolvable microneedle patches (MAPs) were considered as they offer benefits of easy self-administration, simple transportation and are relatively waste-free. In general, they offer enhanced stability, preserved bioactivity of the therapeutic, and longer shelf-life than liquid formulations.

Use of MAPs for delivery of lipid nanoparticle (LNP)-based vaccines and other therapeutics presents various challenges including preserving the bioactivity of these materials when loaded into the system. The inherent instability of LNPs during MAP fabrication can result in aggregation, structure loss and degradation of the active. It is crucial to add appropriate protectants to maintain the essential properties of LNPs within the MAP matrix. This is just one of a wide range of factors that need to be managed to develop a viable MAP product. In this research the main objective was to develop more efficient alternative approaches to conventional formulation screening that is time consuming and expensive. The intention was to create highly scalable procedures, and data-driven approaches that, when combined, provide an ability to rapidly formulate LNP-loaded MAPs that maintain their integrity and stability on storage at ambient temperature. The experimental protocol involved generation of solid formulations of LNPs comprised of mRNA and excipients that were subsequently reconstituted and tested for activity by transfection studies *in vitro*. Transfected cells were stored for 24 hours. All the data generated were normalized and provided input for modeling algorithms designed to predict suitable excipients. These compositions were used for further rounds of experimentation, AI-algorithm prediction, etc., to continuously iterate towards optimized formulations.

A specific example showed encapsulation of a STING agonist (undisclosed) in a LNP increased its targeting properties, potency, and sustained its duration in the systemic circulation, compared to free STING agonist. This material was effective in reducing progression of a model of glioblastoma (EGFRv111-CTZA) in mice. Data efficient screening was conducted to identify excipients able to stabilize the STING-LNPs in microneedle patches. Various factors were included in the algorithm configuration such as: excipient types, constraints, objectives, sample size, batch size, to improve prediction of stability improvements provided by a selection of excipients that included polymers, sugars, and amino acids.

In summary, use of appropriate LNP constructs to encapsulate STING agonists increased their stability and maintained their therapeutic activity as demonstrated by potent activation of the STING pathway *in vitro*. Furthermore, by formulating solid LNPs with suitable excipients it was possible to show maintenance of bioactivity after the water removal process. In performing this work with the use of powerful AI technology, it was possible to identify stable solid-state LNPs for MAPs 12 times faster than conventional formulation approaches. By combining HTS protocols with algorithm-driven approaches it was possible to rapidly design thermostable lipid nanoparticle formulations which the research team anticipates will expand the clinical utility and applications of these advanced drug delivery systems.

As drug delivery complexity increases there is a growing need for more sophisticated approaches to design and evaluation of suitable formulations. This work exemplifies the way forward in utilizing new technologies to aid in the facile identification of viable formulations for more challenging delivery issues.

PATRICK DELUCA EMERGING RESEARCHER AWARD 2025
(YEAR 2)

Effect of Polymer Architecture on Crystal Growth in Amorphous Nifedipine: Bottlebrush vs. Linear Polymer PEGs

Sichen Song, University of Wisconsin-Madison

This study explored the influence of polymer excipient structure for modifying crystallization behavior of amorphous drugs in the solid state. The use of amorphous forms of poorly soluble drugs has proved to be valuable strategy for improving their delivery but crystallization of such systems can adversely affect their intended benefits. Three different bottle brush polyethylene glycol polymers (BB PEGs) were synthesized with varying backbone degrees of polymerization (N_{bb} = 6.0, 56.6, and 107.6) and used to dope nifedipine (NIF) liquid/glass. Crystal growth rates for NIF in the presence of BBB PEGs were determined using thermal stage microscopy at three different temperatures: 303K, 313K, and 323K. Results with the bottlebrush polymers were compared with data generated with a linear PEG having a molecular weight equivalent to that of the BB PEG side chains (1,000 g/mol).

Crystal growth kinetics for nifedipine were less affected by the bottlebrush architecture than by the linear polymers. It was postulated that this was likely due to restricted segmental dynamics in the BB PEGs. As N_{bb} increased, the perturbation to growth rate decreased. Crystal growth rates in NIF liquid/glass were accelerated in the presence of linear PEG versus when BB PEGs were used. In addition, the backbone degree of polymerization was important to the effectiveness of crystallization modification provided by these more elaborate polymers.

This work highlights the value of exploring the crystallization tendency of an amorphous API and describes an effective methodology for ranking the relative benefits of various polymer types for preventing phase transformation of drugs on storage.