THE UNIVERSITY OF KANSAS
Pharmaceutical Chemistry

Physical Pharmacy & Drug Delivery Research Laboratory – Michael J. Hageman, Ph.D.

With 30+ years of experience in industry, academic pursuits will focus on a problem statement driven research program. The labs will focus on Physical Pharmacy and Drug Delivery (P_2D_2) as it relates to understanding physicochemical properties of the drug and the excipients that dictate formulation, process design and bioperformance. The P_2D_2 Labs will have the capability to produce, process, and characterize small molecule, peptide, protein and cellular-based therapeutics as formulated through excipient-stabilized amorphous formulations for either oral or parenteral delivery.

I. Apply processing capabilities based on mini-lab scale spray-drying, lyophilization and vacuum evaporation to generate amorphous materials for investigation, characterization and enhanced delivery of peptides and small molecules.

1) Control dissolution behavior and modulate bioperformance of amorphous solid dispersions (ASD) through careful excipient selection. Examine the ability to enhance oral absorption or normalize a drug's molecular physicochemical properties through generation of amorphous drug formulated in solid dispersions.
2) Define ASD stability/dissolution for ternary systems of drug, polymer and surfactant (e.g. DRUG:HPMCAS:TPGS) as they become quaternary systems upon water uptake during GI transit. Determine the impact of ASD excipient selection and ASD composition for physical stability and dissolution of both peptide and small molecule drugs.
3) Explore the role of excipients in oral modulated release formulations prepared by mini-lab scale fluidized bed coating of ASD spray-layered multi-particulate beads. Couple solubilizing excipients (polymers, surfactants, lipids, cyclodextrins) to create spray layered ASD formulations whose release is subsequently modulated by spray layering of rate controlling polymers for desired rates or locational release in the GI tract.

II. Develop tools to examine the role of solubilized formulations at the physiological interface, understanding the advantages and limitations of excipients used to facilitate supersaturation and para/trans cellular permeation.

1) Identify *in vitro* cell-based methods to screen for the propensity of interstitial and intracellular drug precipitation/crystallization when repeatedly exposed to supersaturated extracellular concentrations.
2) Evaluate the utility of specific cadherin binders (linear & cyclic peptides) to transiently open cellular tight junctions, permitting oral delivery of poorly permeable small molecules, peptides and proteins.
3) Examine the co-delivery and co-localization in the GI tract of permeability enhancing peptides and low permeability drugs (both poorly soluble themselves) using spray-layered and coated multiparticulates.
4) Couple drug solubilization strategies and ASD, specifically targeting localized drug delivery to the lower GI tract and mesenteric lymph. The focus will be for localized, not systemic, treatment of infectious bowel disease (IBD) and tumors with extensive mesenteric lymph bed involvement.

III. Identify mechanisms of, and mitigation strategies for, instability of peptide/protein drugs in lyophilized, foam-dried, spray-dried and spray-layered solids during processing, storage and residence time at the administration site.

1) Develop highly hydrated solids as high concentration solution models to study peptide/protein stability during dehydration, rehydration, and dissolution/diffusion steps. Develop models to examine interfacial-induced destabilization of peptides/proteins during tangential filtration processing and storage.
2) Develop models to study the role of formulation composition and design on peptide/protein stability and release (dissolution/diffusion) from drug-depots at 37°C, mimicking subcutaneous depot release or dosage form release of peptides and proteins following hydration.

IV. Examine processing, stabilization, and formulation of live cells, such as lymphocytes (T cells) for parenteral delivery and also gut microbiota-based, and GI regionally targeted, bacterial therapeutics for oral delivery.

1) Move toward and beyond DMSO-free cryopreservation into stabilization of cells through "reduced hydration" via lyophilization, evaporative-drying, foam drying, and spray-drying. Identify cell preserving excipients, intra- and extracellular, which will maintain cell or bacterial viability upon dehydration and rehydration stresses.
2) Establish oral delivery systems to stabilize microbiota-derived bacteria in those systems using excipients to stabilize and provide GI regional targeted release of bacteria from spray-coated multiparticulates.
3) Examine the role of manufacturing-based shear forces on the stability of cellular based therapeutics.
4) Establish analytical methods, including cellular based integrity assays, to ascertain stability and changes in cellular properties as manifested in cell viability, proliferation and cellular functional attributes.

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