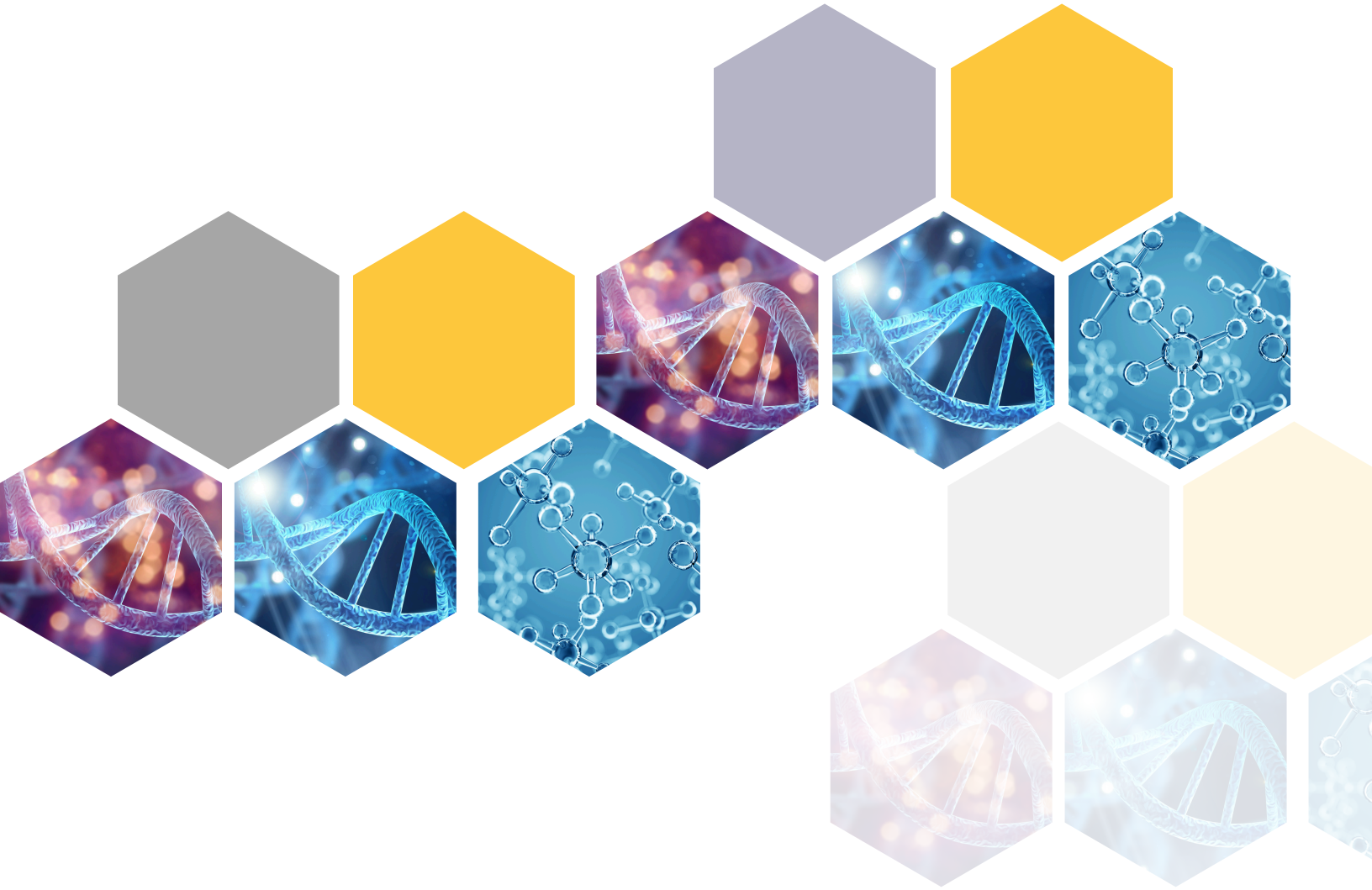
Solubility Matters

The $100 Billion Problem:

Why Solubility Needs a Smarter Approach



IMAGINE biotech.ai

WWW.IMAGINEBIOTECH.AI

I. The $100 Billion Problem: Why Solubility Needs a Smarter Approach

Ninety percent (90%) of current pipeline drugs fall in the two low solubility classes of the Biopharmaceutical Classification System. Solubility is defined as molecular level mixability via intermolecular interactions. Because all drugs in the body show medicinal effects in the form of aqueous solutions, a lower solubility reduces the medicinal effects and bioavailability.

Solubility is, therefore, a critical data point for new drug development and value creation. At the early stages of drug development, the aim is to evaluate the pharmacology, pharmacokinetics and toxicology of a compound using a simple liquid formulation. In selecting excipients which can solubilize a particular compound, the industry currently relies on a very old trial and error-based approach.

This historic reliance on trial and error-based approaches resulted in Contract Development and Manufacturing Organizations (CDMO) maintaining US gross annual revenues of more than $104 billion and projected to grow at a CAGR of 9.3% and all this with a new drug failure rate in excess of 95%. Trial-and-Error approach methods rely heavily on empirical testing of excipients, which is time-consuming and resource-intensive.

This approach requires significant quantities of API and excipients, driving up costs exponentially. Manual approaches like this take longer and demand more labor, driving up costs. High-throughput AI methods can reduce this cost in time delays and dollar wastage.

Technology advancement has provided for the application of a more intelligence-based methodology to formulation development. Available technology provides several approaches that can be used to predict solubility including:

(1) quantum mechanics, (2) the general solubility equation (GSE), and (3) machine learning. Although the physical models underlying simulations are inherently approximations, they have become substantially more accurate and reduce risk of trial and error delays.

Predicting Drug-Excipient Interactions can best be done by using electron energy calculations (e.g., via molecular dynamics simulations) quantifying interactions between drug molecules and solubilizing agents. Measuring the energy of a molecule's electrons helps identify suitable solubilizers for intravenous drug delivery by revealing molecular interactions and stability characteristics critical for formulation design.

Electron density maps identify hydrophobic drug regions that may interact with nonpolar solubilizer components (e.g., Kolliphor® HS 15'slipophilic esters). Energy profiles can also determine how cosolvents (e.g., PEG 300, ethanol) disrupt water's hydrogen-bonding network to enhance solubility. Energy profiles can help stabilize micelle-drug complexes by assessing van der Waals and electrostatic forces, (e.g., Cremophor EL in paclitaxel formulations).

Preventing precipitation is possible with simulations predicting how cosolvents alter micelle hydration and radius of gyration to maintain drug solubility post-dilution. The cost of finding a solubilizer depends on the complexity of the drug molecule, the technologies employed, regulatory requirements, and the efficiency of the screening process. While traditional trial-and-error methods are costly due to their inefficiency, modern approaches like high-throughput screening and computational modeling offer extensive savings by reducing material usage and timelines.

The properties of the API are the primary driver of the technology choice. Knowledge of the API characteristics directly leads to a more intelligent and rational decision as to which technology is most appropriate for any given drug formulation project.

The decision of which approach to follow involves potential development bias and what molecular data that is available. Creating a new novel excipient has its advantages, however, it involves substantial costs to establish regulatory data. With this pathway computational methods can prioritize solubilizers with favorable electron interaction energies, accelerating development of alternatives to problematic agents (e.g., Cremophor EL-free paclitaxel formulations).

Some decision makers look at the FDA and its Inactive Ingredient Database (IID) to reference previously approved inactive ingredients. The thinking being to reduce regulatory scrutiny (and costs) for excipients with established safety profiles. However, the IID provides maximum potency values per unit dose, it does not automatically validate safety for higher excipient concentrations than listed. If an excipient is listed at a comparable potency level, sponsors may avoid extensive toxicological studies, shortening review timelines.

This is particularly important in intravenous routes of administration as maximum potency per unit dose does not equate to maximum Daily Exposure (MDE) unless the product's daily dose is a single unit.

II. Sample problem with intravenous therapeutic routes using KS-J

Please see FDA Inactive Ingredient Database format sample below and complete listing is located at: https://www.fda.gov/drugs/drug-approvals-and-databases/inactive-ingredients-database-download

INGREDIENT_NAME	ROUTE	DOSAGE_FORM	MAXIMU	MAXI	RECORD_U
.ALPHA.-TOCOPHEROL	INTRAVENOUS	INJECTION, POWDER, FOR SUSPENSION			
.ALPHA.-TOCOPHEROL, DL-	INTRAVENOUS	INJECTION, EMULSION	178	mg	
.ALPHA.-TOCOPHEROL, DL-	INTRAVENOUS	SOLUTION, CONCENTRATE			
1,2-DISTEAROYL-SN-GLYCERO-3	INTRAVENOUS	INJECTABLE, LIPOSOMAL			
1,2-DISTEAROYL-SN-GLYCERO-3	INTRAVENOUS	INJECTION	68	mg	
ACETIC ACID	INTRAVENOUS	INJECTION	827	mg	
ACETIC ACID	INTRAVENOUS	INJECTION, POWDER, FOR SOLUTION			
ACETIC ACID	INTRAVENOUS	INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION	3	mg	

To take KS-J and given a total of 506 "intravenous route" listings in IID file the trial-and-error method would cost a minimum of $5,060,000 and take over 10 months of laboratory time.

Using extensive characterization of drug-excipient interactions through molecular modeling (even with all 506 "safe" candidates) can reduce that timeline to one month or less. This should be further shortened by selecting the candidates for molecular modeling with some computational chemistry data sets.

Cosolvents like ethanol or PEG reduce dielectric constants, favoring nonpolar drug solubilization so that category may be eliminated on a first pass. The IID focuses on prior safe use rather than functional classification. A single ingredient (e.g., PEG) may appear multiple times under different dosage forms so many cosolvents are included.

First question for this sample problem is to determine if the KS-J molecule is polar so as to eliminate the cosolvent candidates. To determine this there two key factors, presence of polar bonds and molecular geometry. KS-J contains functional groups like nitro groups (NO_2) and glycosyl groups, which involve atoms with significant electronegativity differences: Nitro groups (NO_2): Oxygen (3.44) is more electronegative than nitrogen (3.04), creating polar N=O and N-O bonds. Glycosyl groups: Oxygen atoms in these groups form polar C-O and O-H bonds due to their higher electronegativity compared to carbon and hydrogen.

Reviewing the KS-J molecular geometry it is asymmetrical because: The nitro and glycosyl groups are arranged in a way that prevents bond dipoles from canceling. Lone pairs on oxygen and nitrogen atoms disrupt symmetry, contributing to a net dipole moment.

Since KS-J has polar bonds and an asymmetric geometry, it is a polar molecule. This polarity arises from uneven electron distribution caused by electronegativity differences and the lack of symmetry to cancel out dipoles.

The second question is does the KS-J molecule have poor lipid solubility and if so, lipid formulation candidates are excluded. KS-J solubility in polar solvents shows DMSO at: 9.3 mg/mL and DMF at: 0.5 mg/m.

With poor lipid solubility candidates lipid formulations will be complex because of the number of additives required to meet performance objectives so those candidates will be secondary.

Deliverables will require computational methods tests to prioritize solubilizers that are not lipid or (polyethylene glycols) (PEG) that have favorable electron interaction energies on the remaining non cosolvent and non-lipid formulation excipient candidates.

The drug-excipient interactions will be performed using MD/QM simulations but not including GRAS agents in combinations. IV-Specific Optimization and pH adjustment will target physiological range (5-8) using minimal buffer capacity. A complete report prioritizing the candidates will include suggested dosage maximation data.

Cosolvents like ethanol or PEG reduce dielectric constants, favoring nonpolar drug solubilization so that category may be eliminated on a first pass. The IID focuses on prior safe use rather than functional classification. A single ingredient (e.g., PEG) may appear multiple times under different dosage forms so many cosolvents are included.

First question for this sample problem is to determine if the KS-J molecule is polar so as to eliminate the cosolvent candidates. To determine this there two key factors, presence of polar bonds and molecular geometry. KS-J contains functional groups like nitro groups (NO_2) and glycosyl groups, which involve atoms with significant electronegativity differences: Nitro groups (NO_2): Oxygen (3.44) is more electronegative than nitrogen (3.04), creating polar N=O and N-O bonds. Glycosyl groups: Oxygen atoms in these groups form polar C-O and O-H bonds due to their higher electronegativity compared to carbon and hydrogen.

Reviewing the KS-J molecular geometry it is asymmetrical because: The nitro and glycosyl groups are arranged in a way that prevents bond dipoles from canceling. Lone pairs on oxygen and nitrogen atoms disrupt symmetry, contributing to a net dipole moment.

Since KS-J has polar bonds and an asymmetric geometry, it is a polar molecule. This polarity arises from uneven electron distribution caused by electronegativity differences and the lack of symmetry to cancel out dipoles.

The second question is does the KS-J molecule have poor lipid solubility and if so, lipid formulation candidates are excluded. KS-J solubility in polar solvents shows DMSO at: 9.3 mg/mL and DMF at: 0.5 mg/m.

With poor lipid solubility candidates lipid formulations will be complex because of the number of additives required to meet performance objectives so those candidates will be secondary.

Deliverables will require computational methods tests to prioritize solubilizers that are not lipid or (polyethylene glycols) (PEG) that have favorable electron interaction energies on the remaining non cosolvent and non-lipid formulation excipient candidates.

The drug-excipient interactions will be performed using MD/QM simulations but not including GRAS agents in combinations. IV-Specific Optimization and pH adjustment will target physiological range (5-8) using minimal buffer capacity. A complete report prioritizing the candidates will include suggested dosage maximation data.