Depot Injection Formulation and Modelling – Part B

Application for Formulation Scientists
In developing an oil-based depot formulation, formulation scientists can leverage the understanding of diffusion principles and partition coefficients to optimise drug release profiles and ensure effective therapeutic outcomes.

This information is utilised to:

1. **Select the Right Excipients:**
   The oil-water partition coefficient (Kow) is crucial for choosing appropriate excipients that will influence the drug's release rate. If a slow, sustained release is desired, a high Kow indicates that the drug is more lipophilic and will remain longer in the oil phase, so formulators should select oils or lipids that enhance this property. Conversely, for a faster release, a low Kow is preferable, and formulators would choose excipients that facilitate rapid partitioning into the aqueous phase.

Tip: Some co-solvents and surfactants may also diffuse out of the depot into the surrounding tissues. This in turn can impact drug release. If the primary impact is on the saturation solubility, then the result will most likely be an increase in the drug release rate as long as the concentration of dissolved drug is not impacted. Conversely, if the solubility is reduced to the point where precipitation occurs then the overall drug release would be expected to slow. The impact may be derived from changes to Kow or the diffusion kinetics. Because of this it is a good idea to understand the solubility and partition coefficient of your excipients when making formulation selections, and to evaluate this aspect of the formulation as part of the formulation design space.

2. **Design the Depot Structure:**
   Understanding diffusion coefficients and Fick's laws helps scientists design the depot's physical structure. By predicting how the drug diffuses through the oil phase and into surrounding tissues, they can adjust the viscosity of the oil, the drug particle size (if in suspension), and other formulation parameters to control the release rate. For instance, increasing the viscosity of the oil phase can slow down the drug's diffusion rate. Conversely reducing the drug's particle size can increase how quickly it is released from the depot.

3. **Prototype Selection:**
   Mathematical models, including Fick's laws and partitioning relationships, can be used to predict how the drug will be released. Formulation scientists can use these models to simulate drug release profiles and adjust formulation parameters to achieve the desired release kinetics. This includes setting up experiments to measure actual release rates and compare them with predicted models to fine-tune the formulation.

4. **Address Biological Factors:**
   While biological factors like blood flow, tissue permeability, and enzymatic activity can be challenging to control, understanding their impact helps scientists anticipate how these variables might affect drug release. By simulating different biological conditions and incorporating potential variations into their models, scientists can develop formulations that are robust and effective under various physiological conditions.

5. **Route of Administration**
   The selection of the target injection site significantly impacts the pharmacokinetics and effectiveness of long-acting injectable (LAI) formulations.[5] Intramuscular (IM) injections generally offer faster absorption and better depot stability compared to subcutaneous (SC) injections, due to higher blood flow and tissue characteristics. However, the site can also influence the variability in drug release, with factors like body composition, muscle activity, and local blood flow playing crucial roles in how the drug is absorbed and released over time.

Additionally, the choice of site affects patient comfort, risk of local reactions, and long-term consistency of drug delivery. Injection site considerations must align with the drug's formulation properties, such as viscosity, release mechanisms, and dose volume, to ensure optimal therapeutic outcomes. By carefully selecting the injection site and tailoring the formulation to the target route the formulator can better control the release profile and efficacy of the drug, while minimising adverse effects and improving patient adherence.

6. **Optimise Drug Loading:**
   The partition coefficient and diffusion models guide scientists in determining the optimal drug concentration in the oil phase. They ensure that the drug loading maximises therapeutic efficacy while maintaining the desired release profile. This involves balancing the drug's solubility in the oil phase with its intended release rate.

7. **Designing for Specific Therapeutic Needs:**
   For chronic conditions requiring steady drug levels, scientists can use their understanding of diffusion and partitioning to design formulations that provide controlled release over weeks or months. For situations requiring rapid therapeutic action, they can adjust the formulation to facilitate quicker drug release into the bloodstream.

Experimentally there are several ways to tackle the formulation approach. The following example outlines one approach for development of an oil-based solution.

Evaluating the Saturation Solubility

For selecting suitable candidate solvents, the saturation solubility must be known. The most obvious reason is that the target drug concentration (or load) must be supported by the drug solubility in the selected solvent. Typically, the target drug load should not exceed 85% of the saturation solubility; drug loading too close to the saturation solubility limit can lead to precipitation on long term storage. The drug concentration relative to saturation can also impact drug release because the concertation gradient which drives passive diffusion is impacted by the relative solubility in each phase.

To measure the saturation solubility an excess of drug is added to each solvent and mixed continuously until equilibrium is reached, typically 24 to 48 hours. The samples are centrifuged or filtered to remove the undissolved drug, and the samples are assayed for the content of dissolved drug. To assess all aspects of the formulation this study should be performed twice. For relevance to the drug product storage stability this should be performed at the temperature specified for long term storage. For relevance to the drug release the solutions should be maintained at 37°C to mimic the biological conditions.

Tip: It is a good idea to design the experiment with at least ten candidates consisting of pure solvents (oils) as well as complex solvent systems which include varying types and compositions of co-solvents and surfactants. This will not only save time compared to an iterative approach, but if designed correctly using multivariate analysis, the solubility effects may be used to identify more optimal candidates or compositions which may not have been included in the experimental design. Additionally, if the target dose is known then performing the screening based on target concentration will narrow down the list of solvents, cosolvents and surfactants and will help to design a robust composition.

Determining the Oil/Water Partition Coefficient

The most common method for estimation of the partition coefficient is the "shake flask method." But for the context of formulation development the procedure is altered compared to the traditional LogP or Kow which is typically performed using pure water and an immiscible solvent such as Octanol. To simulate the biorelevant conditions the drug is dissolved in the candidate solvent(s) at the target concentration for the drug product. The solvent is added in equal portions with phosphate buffered saline (pH 7) in an appropriate shaker flask. The flask is mechanically shaken for a period sufficient to allow equilibration and then allowed to stand undisturbed for at least 2 hours which allows the phases to separate. Samples are collected from both the oily and aqueous phases and assayed for the content of dissolved drug. The partition coefficient (K) is calculated as the concentration of drug in the oily phase divided by the concentration of drug in the aqueous phase. It is typically calculated as the mole/L ratio, but for the purposes of formulation assessment the mass/vol (g/L, or mg/L) may also be used.

Tip: The partitioning must reach equilibrium to accurately determine the Kow. To ensure equilibrium is reached it is best to test multiple shaking times using separate samples. The relative concentration in each phase can be compared between time points to determine when equilibrium is reached.

Estimating Steady-State Diffusion/Drug Release

Experimentally, the flux can be measured as the change in total drug release over time per unit surface area. Using USP dissolution apparatus II with semi-solid enhancer cells has demonstrated discriminatory capability and biorelevance for drug release of long-acting injectable formulations (LAIF).[1,2] The drug product is added to the enhancer cell dosing chamber and covered with a hydrophilic filter member (0.45 µm) which simply retains the dose inside the cell.[3] Biorelevant media, simulated interstitial fluid or PBS pH 7, maintained at 37°C is used as the receiving media. The enhancer cell is submerged in the dissolution vessel and drug release is monitored with constant stirring (25 or 50 RPMs) by taking samples of the receiving media at specified time intervals. Some screening may be required to determine the best sampling interval and total analysis time. Drug release presents as an intrinsically curved line. As the total concentration of the drug in the applied dose is released, the concentration gradient decreases, and thus the flux also decreases; this gradually tapers to zero as drug release reaches equilibrium. The sampling interval and total analysis time needs to be sufficient to identify and capture at least five points of the linear portion of the profile for analysis of steady state diffusion.

The flux can be estimated from the drug release as single point from the total drug diffused/released into the receiver cell at a specified time point. Given the equation:

$$R_{(t)} \approx J_{(t)} = \frac{dc_a}{dt} * \frac{V}{A} \Big/_{x=0} \cdot K_{ow}$$

Where:

- dca is the measured concentration (µg/mL) of drug in the receiver media at time (t) in minutes.
- V is the total volume of the receiving vessel in mL (cm^3).
- A is the surface area of the drug product exposed to the receiving media (cm^2).

The flux can also be determined from multiple points along the drug release profile. There must be several points, preferably at least five, along the linear portion of the profile, and prior to the asymptote. The slope of the line represents the change in concentration over time (dc/dt). This method also allows you to evaluate the linearity of the drug release and should be ≥ 0.95. From the example graph (Figure 2) the flux may be estimated as per the equations below where the drug release concentration at 240 hours is measured at 1.2138 µg/mL, the total volume is 500 mL, and the exposed surface area is 2 cm^2.

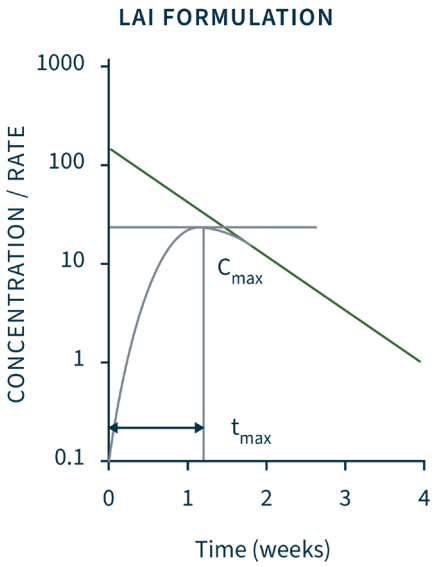


Figure 2: Typical pk profile for a long-acting injectable formulation

Single Point:

$$J_{(t)} = \frac{1.2138\ \mu g/cm^3}{14{,}400\ min} * \frac{500\ cm^3}{2\ cm^2} = 0.0211\ \frac{\mu g}{cm^2 * min}$$

Or where multiple points are used to determine the slope of the line for the total drug release.

Multi-Point:

$$J_{(t)} = \frac{0.03637\ \mu g/min}{2\ cm^2} = 0.0182\ \frac{\mu g}{cm^2 * min}$$

The data obtained from this type of experiment are indicative of the combined diffusion and partition characteristics of the drug in the specified system. This also assumes that the drug is rapidly cleared away from boundary interface. Because the diffusion and partition characteristics cannot easily be separated, they can be combined and considered together in terms of the drug's diffusion coefficient relative to the specific formulation. These data can then be used to compare solvents/solvent systems or prototype formulations. While additional modeling might be required to develop IVIVC for direct evaluation of *in vivo* drug release, the relative *in vitro* drug release can be used to maximise or minimise drug release rate. Or assess potential changes in the drug release resulting from formulation changes.

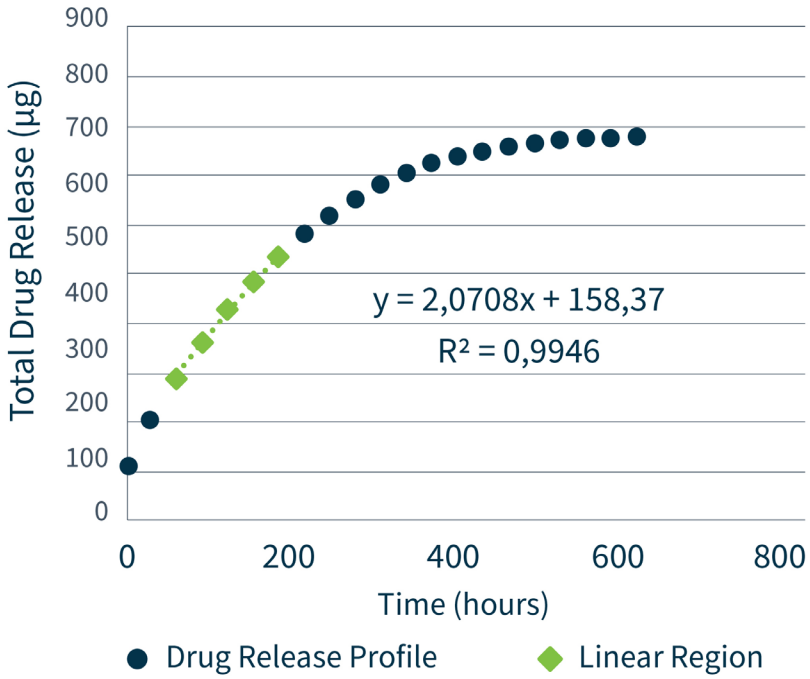
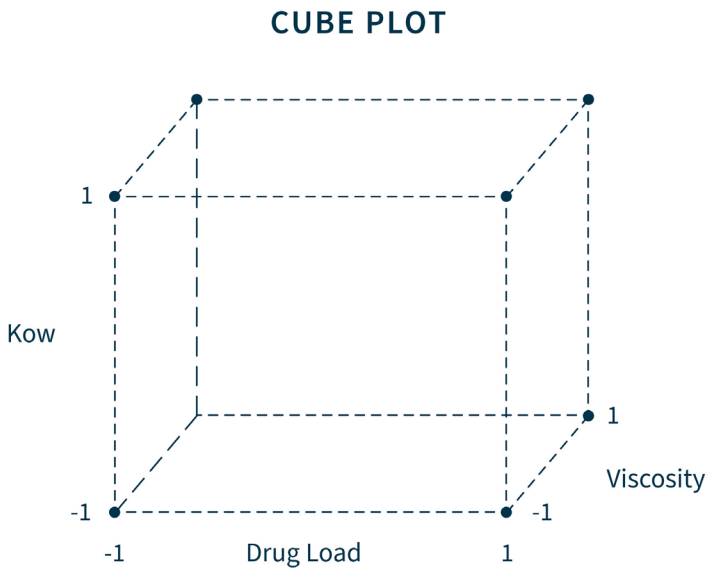


Figure 3: Example LAI drug release profile



Viscosity	Drug Load	Kow
1	-1	-1
-1	1	-1
1	-1	1
1	1	-1
-1	1	1
-1	-1	-1
1	1	1
-1	-1	1

Figure 4: Example 2-level split factorial formulation design space DOE

Tip: The clearance can be investigated by altering the stirring speed of the receiving media to more closely simulate static distribution/diffusion in the aqueous phase. It should be noted that *in vivo* that body movement can aid in distribution of the drug so the target injection site should be considered when selecting the *in vitro* conditions.

Optimising Prototypes

By applying these mathematical principles and diffusion models, formulation scientists can develop oil-based depot injections to target specific therapeutic needs, offering controlled, sustained, or rapid release as required. During the preformulation phase these data may be used to select solvents and co-solvent/surfactant compositions by assessing the primary effects on Kow, and solubility; and translating those effects to the impact on drug release through regression analysis.

After the initial prototype formulation has been identified, optimisation can be performed through DOE(s) by altering critical formulation parameters such as Kow, viscosity, density, or drug load. The resulting impact on drug release is evaluated. The primary effects and/or interactions are used to develop formulation models, optimise drug release, evaluate the formulation design space, or develop the IVIVC if *in vivo* drug release data are available to reference. This approach ensures that the drug is delivered effectively and safely, optimising patient outcomes and compliance.

Conclusion

The diffusion of a drug from an oil-based depot injection is a complex process influenced by the drug's physicochemical properties, the characteristics of the oil, and the biological environment of the injection site. Understanding these factors helps in designing depot injections that provide a controlled and sustained release of the drug. The mathematical models discussed, including Fick's laws of diffusion and the oil-water partition coefficient are invaluable for excipient selection and formulation development in oil-based drug delivery systems. Fick's laws help predict the rate at which a drug diffuses from the oil phase into the aqueous environment, which is crucial for controlling release profiles. The partition coefficient indicates how the drug distributes between the oil and water phases at equilibrium, informing choices that optimise drug solubility, stability, and release rate. By integrating these models, formulators

can select excipients that maintain the desired drug concentration gradient, achieve targeted release rates, balance solubility and stability, and predict *in vivo* behaviour. This ensures that the developed formulations meet specific therapeutic goals, providing controlled and sustained drug release or rapid onset as needed.

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Travis Webb comes to Pii with over 17 years of experience in both analytical and formulation contract development across multiple dosage forms including injectables, liquid pulmonary, oral solids and liquids, and topical drug products. During his career he has developed over 20 approved drug generic and NDA drug products and helped bring numerous INDs to various clinical stages. Travis also has extensive experience with QBD and pediatric drug product development for both the U.S. and Europe, supporting IND/NDA filings and communicating with regulatory agencies. Travis holds an M.S. in Pharmaceutical Chemistry from the University of Florida and a B.S in Biochemistry from Troy University.