Depot Injection Formulation and Modelling (Part A)

The development of oil-based long-acting injectable formulations (LAIF) involves creating a formulation where an active drug is dissolved or suspended in an oil-based medium, allowing for a sustained release of the drug over an extended period. These formulations are generally administered intramuscularly or subcutaneously and are designed to provide long-lasting therapeutic effects, reducing the frequency of administration compared to immediate-release formulations. They are particularly desirable in chronic conditions requiring steady medication levels, enhancing patient compliance, and improving treatment outcomes. Oil-based depot injections can also provide localised delivery of drugs, minimising systemic side effects.[1] Although typically used for controlled release, in some cases, the choice of an oil-based formulation may also be driven by the poor solubility of the drug in aqueous solutions, even when a faster release is the target.

Understanding the principles of diffusion is essential for optimising the performance of oil-based injectable formulations. The diffusion process governs how the drug moves from the oil phase into the surrounding aqueous environment of the body, influencing the release rate and overall efficacy of the formulation. By applying mathematical models of diffusion and the oil-water partition coefficient (K_{ow}), formulators can make informed decisions regarding excipient selection and formulation design, ensuring that the drug is released in a controlled and predictable manner to achieve the desired therapeutic effect.

Background

When an oil-based solution is injected into the body, typically intramuscularly, it forms a depot or reservoir at the injection site. This depot releases the drug at a slower rate due to the oil-based nature of the solution. The release process involves diffusion, which is the movement of molecules from an area of higher concentration (the depot) to an area of lower concentration (the surrounding tissues). This process is driven by the concentration gradient and influenced by the oil-water partition coefficient (Kow) of the drug.

The diffusion coefficient (-D) plays a crucial role in determining the rate at which drug molecules move through the medium. Factors affecting the diffusion coefficient include the size and shape of the drug molecules, the viscosity of the oil, and the temperature. There are two primary mechanisms for drug release from an oil-based depot: passive diffusion and partitioning/redistribution. Passive diffusion, driven by the concentration gradient, is the main mechanism, while partitioning between the oil phase and the aqueous environment of the body tissues also occurs. Once the drug diffuses into the aqueous phase, it can be taken up by surrounding tissues or enter the bloodstream.

The diffusion process can be described mathematically according to Fick's first law of diffusion which describes steady-state diffusion, where the flux (amount of free/dissolved drug per unit area per unit time) is proportional to the concentration gradient.[2]

Fick's First Law (Steady-State Diffusion)

$$J = -D\frac{dc}{dx}$$

Where:

- J is the diffusion flux (amount of substance per unit area per unit time) – µg/min*cm^2.
- D is the diffusion coefficient of the drug in the specified matrix.
- dC/dx is the instantaneous concentration gradient.

It is important to note that the concentration gradient described the concentration gradient of the free/dissolved drug. The system becomes more complicated if the drug is micelle or colloid bound, or is in solid state (suspension). In these cases, the equilibrium constant for the bound drug vs free drug and/or the dissolution rate for the suspended drug must be considered as this impacts the effective concentration gradient. While this topic is not discussed in detail here, I have provided some references for further reading.[3,4]

Fick's second law allows for evaluation of diffusive properties in a more real-world situation as it pertains to drug release because the drug concentration changes over time. But this is a much more complicated analysis compared to steady state diffusion and involves a number of steps and use of differential equations. For practical purposes formulations can be effectively evaluated and compared using steady state diffusion.

Fick's Second Law (Non-Steady-State Diffusion)

Fick's second law allows for evaluation of diffusive properties in a more real-world situation as it pertains to drug release because the drug concentration changes over time. But this is a much more complicated analysis compared to steady state diffusion and involves a number of steps and use of differential equations. Fick's second law is better suited to describe drug release over longer periods because as more of the drug is released from the depot an internal concentration gradient will form within the oily phase as the dose is depleted. But for practical purposes formulations can be effectively evaluated and compared using steady state diffusion.

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2}$$

- $\partial C/\partial t$ is the change in concentration over time, where t is time.
- $\partial^2 C)/\partial x^2$ is the spatial change in concentration, where x is the spatial coordinate.

Oil and Water Partition Coefficient

The oil-water partition coefficient is a measure of how a compound distributes itself between a hydrophobic (oil) phase and a hydrophilic (water) phase at equilibrium.

$$K_{ow} = \frac{C_{oil}}{C_{aqueous}}$$

Where:

- K_{ow} is the oil-water partition coefficient.
- C_{oil} is the concentration of the drug in the oil phase at equilibrium.
- C_{water} is the concentration of the drug in the aqueous phase at equilibrium.

In the context of an oil-based depot injection, the partition coefficient plays a crucial role in determining how the drug will

release from the oil phase into the aqueous phase in the tissue. A higher Kow indicates the drug is more lipophilic (oil-loving) and will tend to stay longer in the oil phase, resulting in a slower release. Conversely, a lower K_{ow} indicates the drug is more hydrophilic (water-loving) and will diffuse more readily into the aqueous phase, leading to a faster release.

Biological Factors

Several biological factors significantly influence the diffusion process, including blood flow, tissue permeability, and enzymatic activity. Increased blood flow around the injection site can enhance the rate of drug removal from the depot, speeding up diffusion, while low blood flow can slow it down. The permeability of surrounding tissues affects how easily the drug can move through them, with higher permeability allowing faster diffusion. Additionally, enzymatic activity at the injection site or in surrounding tissues can metabolise the drug, impacting the overall diffusion and release rate.

The rate of drug diffusion from a depot injection can also vary based on whether it is delivered subcutaneously (SC) or intramuscularly (IM). Generally, intramuscular injections allow for quicker delivery and distribution of the drug compared to subcutaneous injections. This is because muscles are highly vascular structures, and IM absorption occurs by drug diffusion from interstitial fluid and capillary membranes into plasma. On the other hand, drugs injected subcutaneously must diffuse through the subcutaneous tissue to reach capillaries and then be absorbed into the systemic circulation. Consequently, the onset of action is longer with subcutaneous administration than with IM administration. Additionally, if the subcutaneous tissue is rich in adipose, drug absorption can be further prolonged, especially with repetitive dosing.

While biological factors may not be easily accounted for, especially when developing a formulation for a new drug that may have limited in vivo permeability data, controlling the formulation parameters can still provide invaluable information for selecting the appropriate formulation.

Mathematical Model in the Context of Drug Release

To model the release of a drug from an oil-based depot, the following factors need to be considered:

1. Diffusion from the oil phase to the aqueous phase.
2. Partitioning between phases.
3. Movement through the aqueous environment

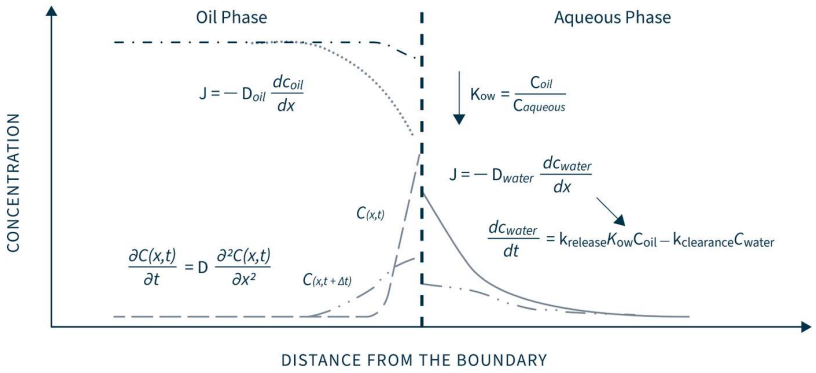


Figure 1: A simple illustration of steady state vs non-steady state diffusion between two phases

The release rate of the drug can be described using a combination of diffusion equations and partitioning relationships. Where the diffusion of the drug from the oil depot to the surrounding tissues is described by Fick's first law of diffusion such that:

$$J = -D_{oil}\frac{dc_{oil}}{dx}$$

At the interface between the oil and aqueous phases, the partition coefficient determines the equilibrium concentrations, or in essence, the tendency of the drug to partition from one phase to the other. This relationship can be used to link the concentrations in the two phases. Once the drug has partitioned into the aqueous matrix of the surrounding tissues it creates an area of higher concentration immediately around the margins of depot. This can saturate the surrounding fluids and the drug must diffuse away from the oil phase before more drug can partition out of the depot. This can also be described according to Fick's first law.

$$J = -D_{water}\frac{dc_{water}}{dx}$$

The combined mathematical model for the release rate (R) of the drug from the oil-based depot can be described as:

$$R(t) = -D\frac{dc_{oil}}{dx}\Big/_{x=0} \cdot K_{ow}$$

The graph (Figure 1) provides a visual example of kinetics as it is related to drug diffusion and partitioning between two immiscible phases. For a period after injection relatively steady state diffusion is dominant and the concentration throughout the depot is roughly uniform. At some distance from the boundary layer there will be a concentration gradient that forms due to the drug partitioning into the surrounding tissues. The magnitude of the gradient will be impacted by both constants, the oil/water partition coefficient, and the rate clearance from the surrounding tissues. As drug release continues non-steady state kinetics will begin to dominate as the drug is in the depot is depleted. At this point, the drug release will slow exponentially in correlation with time. The results in a pK profile similar to Figure 2.

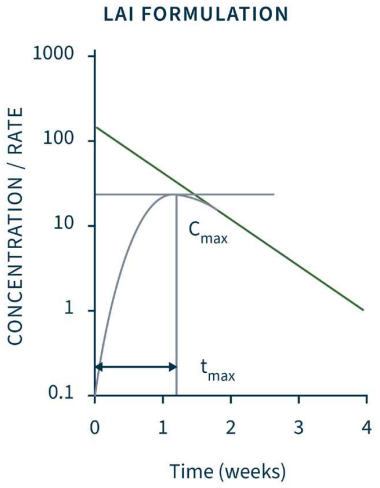
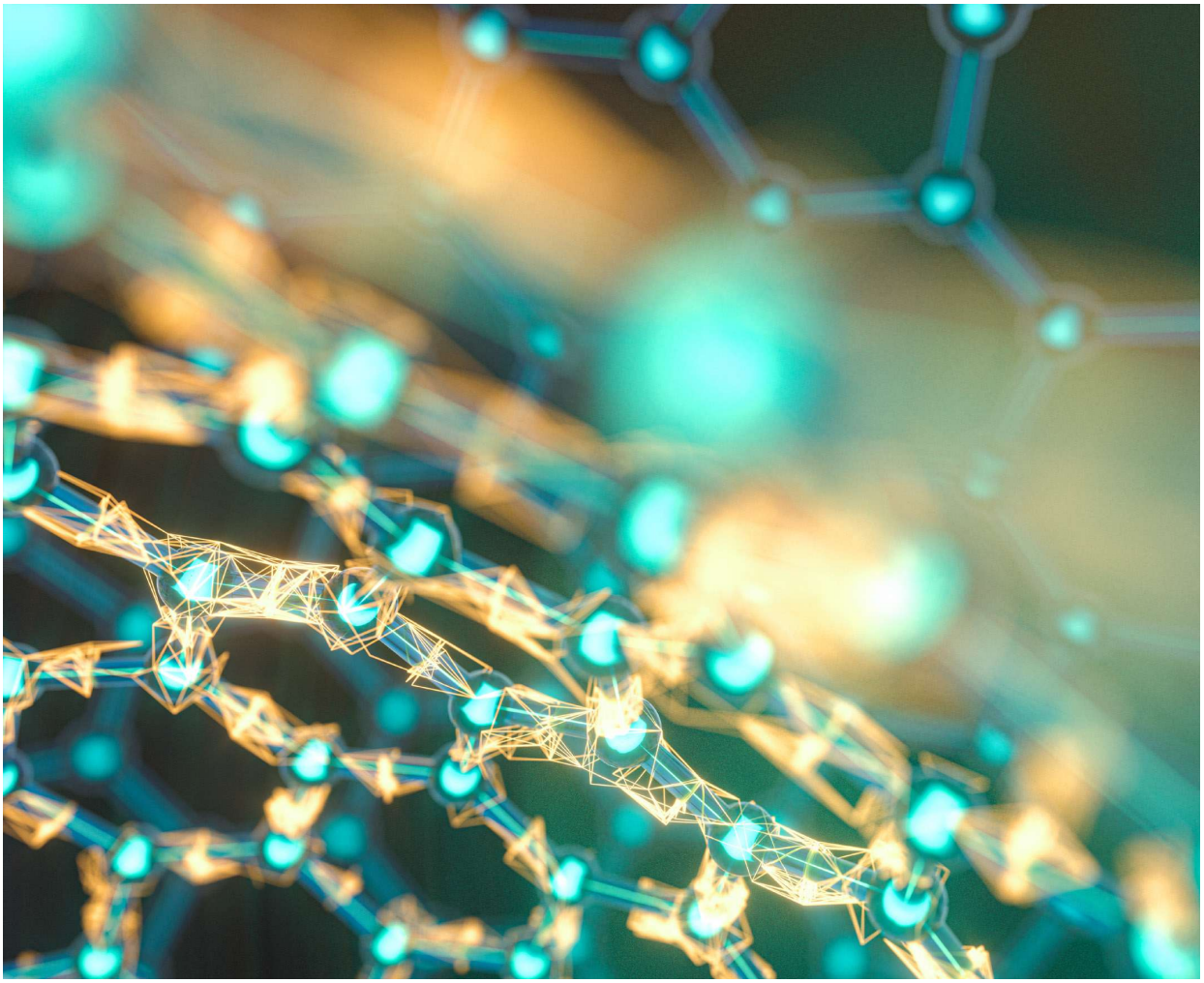


Figure 2: Typical pk profile for a long-acting injectable formulation[5]



To describe the change in drug concentrations and release from the drug product over longer periods of time, we can use differential equations:

$$\frac{dc_{oil}}{dt} = -k_{release}C_{oil}$$

$$\frac{dc_{water}}{dt} = k_{release}K_{ow}C_{oil} - k_{clearance}C_{water}$$

Where:

- $k_{release}$ is the rate constant for release from the oil phase.
- $k_{clearance}$ is the rate constant for clearance from the aqueous phase.

The corresponding pk profile (Figure 2) can be modelled as per.

To be continued in the Spring Issue 2025

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