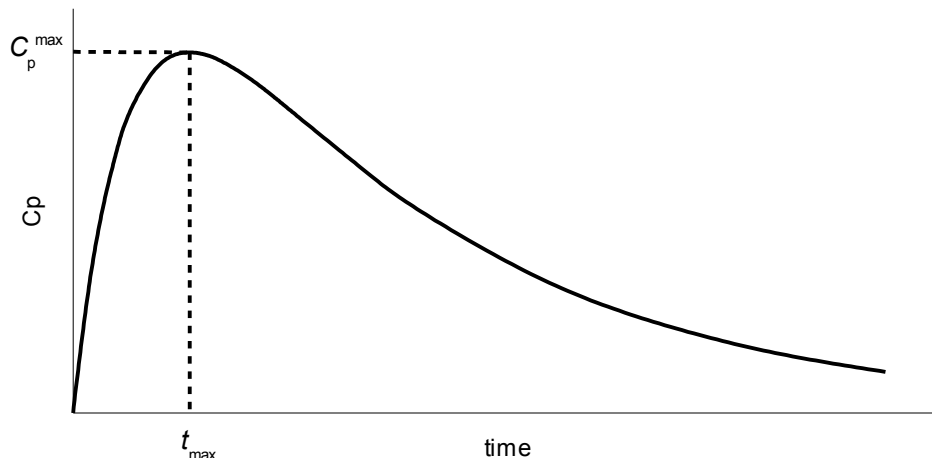


We have now laid enough foundation to move from an IV bolus to oral delivery. Oral delivery is more complicated because the drug must be absorbed from the gastrointestinal tract and withstand the metabolic before reaching general circulation. A typical C_p -time curve for an oral drug is shown below. The curve demonstrates how the rise in concentration as the drug is absorbed followed by the eventual drop in concentration as the drug is cleared. The peak in concentration, $C_p^{\max}$, occurs at $t_{\max}$, which is a standard pharmacokinetic parameter that is listed with oral drugs.

C_p vs. time - oral dose



The formula for C_p is more complicated for an oral drug and adds two new variables – bioavailability (F) and the absorption rate constant (k_{ab}). We have already talked about bioavailability, the fraction of an administered dose that actually reaches general circulation. k_{ab} , with units of inverse time, is a rate constant and almost always larger than k_{el} .

$$C_p = \frac{FD_o}{V_d} \cdot \frac{k_{ab}}{(k_{ab} - k_{el})} \cdot (e^{-k_{el}t} - e^{-k_{ab}t})$$

Before a drug is tested in an oral form, it will have already been dosed as an IV bolus. That means the variables k_{el} and V_d will already be known. That leaves F and k_{ab} to be determined. k_{ab} can be calculated from $t_{\max}$, which can be estimated from the curve. The calculation of k_{ab} is not exact, but it can be estimated by trial-and-error. Keep in mind that k_{ab} is virtually always larger than k_{el} .

$$t_{\max} = \frac{\ln k_{el} - \ln k_{ab}}{k_{el} - k_{ab}}$$

Calculating F requires more work. It is possible that F might be known from the IV bolus. If renal clearance is zero, then total clearance can be used to determine the hepatic extraction

ratio (E_H) and then bioavailability (F). If F is not known, then it will need to be estimated from AUC data and the trapezoidal rule.

The trapezoidal rule is actually easier to apply to oral drug data because one does not need to estimate C_p^0 . C_p^0 for an oral drug is 0. For a specific drug, the AUC of the oral form can be compared to the AUC of the IV bolus to determine F . If the two formulations are administered in different doses, then the dose amounts can be used to normalize the data in the calculation.

$$F_{\text{oral}} = \frac{\frac{AUC_{\text{oral}}}{D_o^{\text{oral}}}}{\frac{AUC_{\text{IV}}}{D_o^{\text{IV}}}}$$

The calculated F is specific to oral administration and is often reported as **oral bioavailability** (F_{oral}). Other non-IV routes of administration (e.g., intramuscular injection, nasal, transdermal, or inhalation) have their own distinct bioavailability. Each is calculated by comparing the AUC of a dose from one administrative route to AUC_{IV} .