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Average Slope vs. Cmax: Which Truly Reflects the Drug-Absorption Rate?

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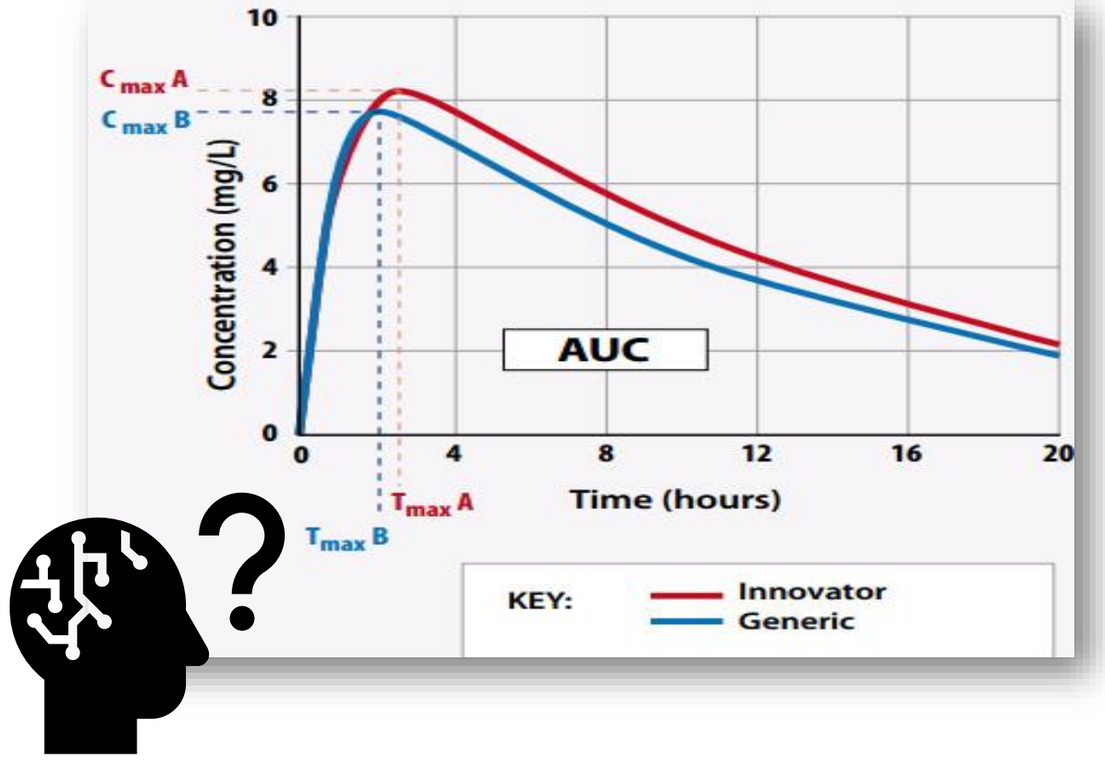
1. Background-Aim

Bioequivalence testing is essential in pharmaceutical development to confirm that two drugs, the Test and Reference products, with identical active ingredients, show similar in vivo performance and therapeutic effects.

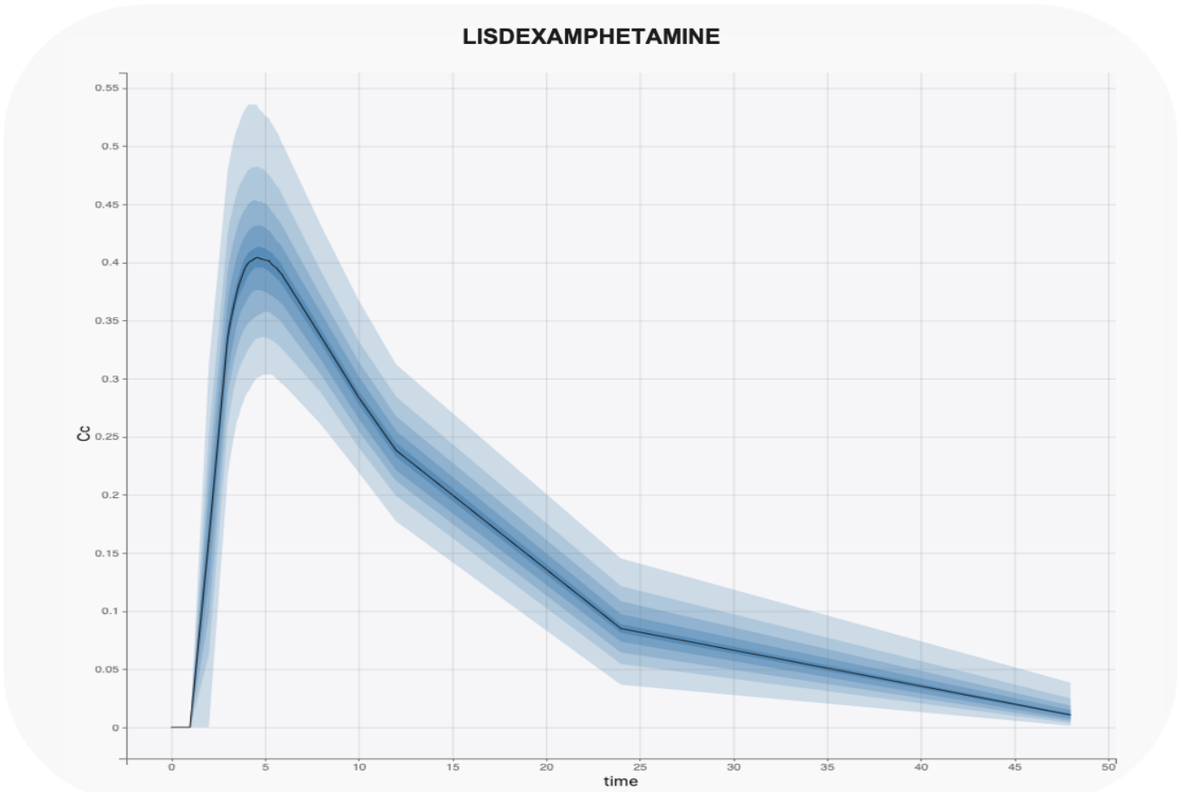
There is **skepticism about the adequacy of Cmax** alone in evaluating absorption kinetics comprehensively. Recent studies using **machine learning (ML) methodologies** aim to improve BE assessments by identifying new metrics for absorption kinetics, such as **average slope (AS).**

This is the first study using modern **ML and deep-learning techniques** to compare the newly proposed metric AS, with the traditional Cmax for assessing drug absorption rates in BE studies.



2. Materials & Methods

Five drugs with diverse pharmacokinetic profiles — nintedanib, methylphenidate, nitrofurantoin, lisdexamfetamine, and theophylline — were selected for analysis.



A **population pharmacokinetic (PK) modeling approach** was employed to generate concentration-time (C-t) data for these five drugs in a simulated population of 1,000 virtual subjects.

Using the **non-compartmental approach** (NCA), classic PK parameters such as Cmax, Tmax, AUC, and AUCinf were estimated from the simulated data.

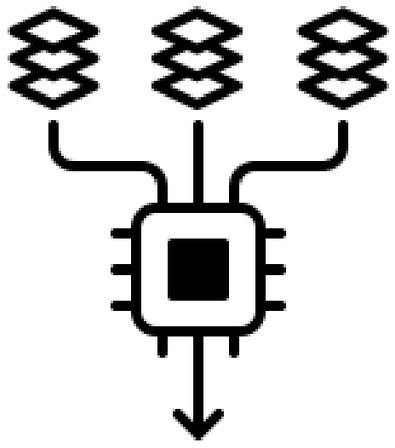
Lisdexamfetamine, having intermediate PK performance (e.g., Tmax, elimination of half-life values) compared to the other four drugs, served as the lead drug for our analysis.

2. Materials & Methods

Additionally, the **AS** for each drug and individual was calculated using the following equation :

$$AS = \frac{\sum_{i=1}^{n-1} \frac{C_{i+1} - C_i}{t_{i+1} - t_i}}{n - 1}$$

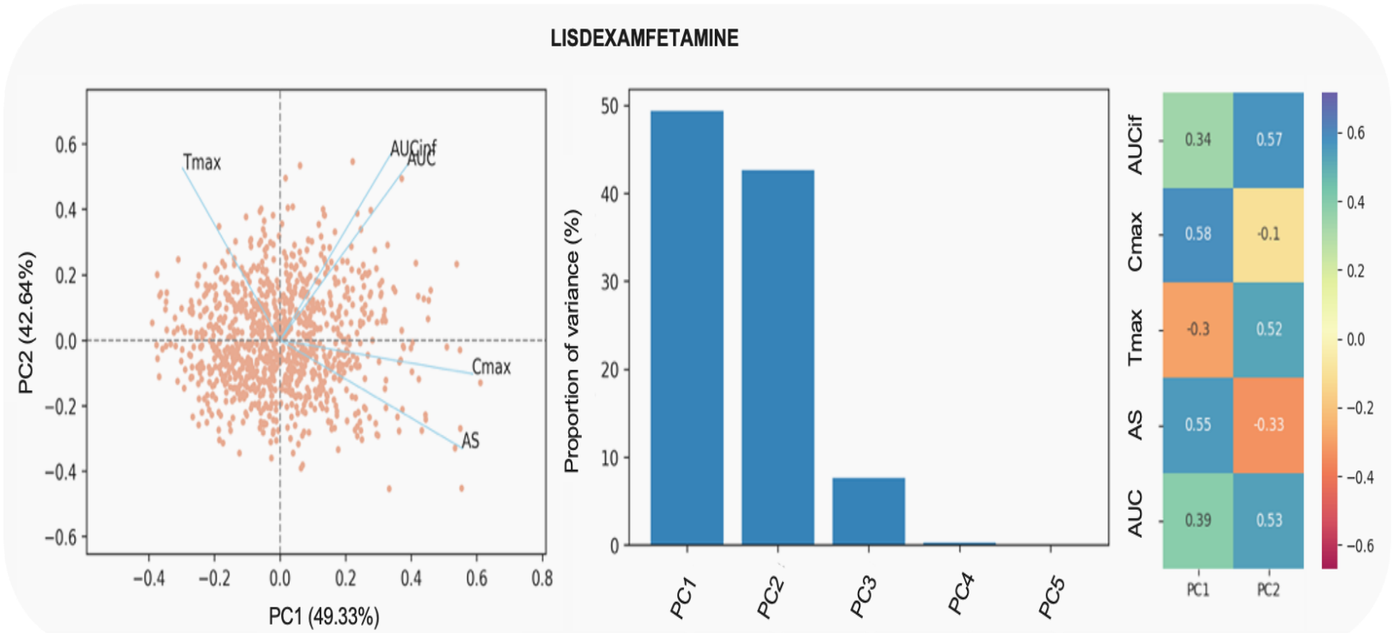
where the n is the number of sampling points up to Tmax, t_{i+1} and t_i refer to two sequential time points, and C_{i+1} and C_i refer to two sequential concentration values.



After generating the BE data, a combination of ML methods was used to thoroughly analyze the data and determine the most suitable metric for expressing drug absorption rates.

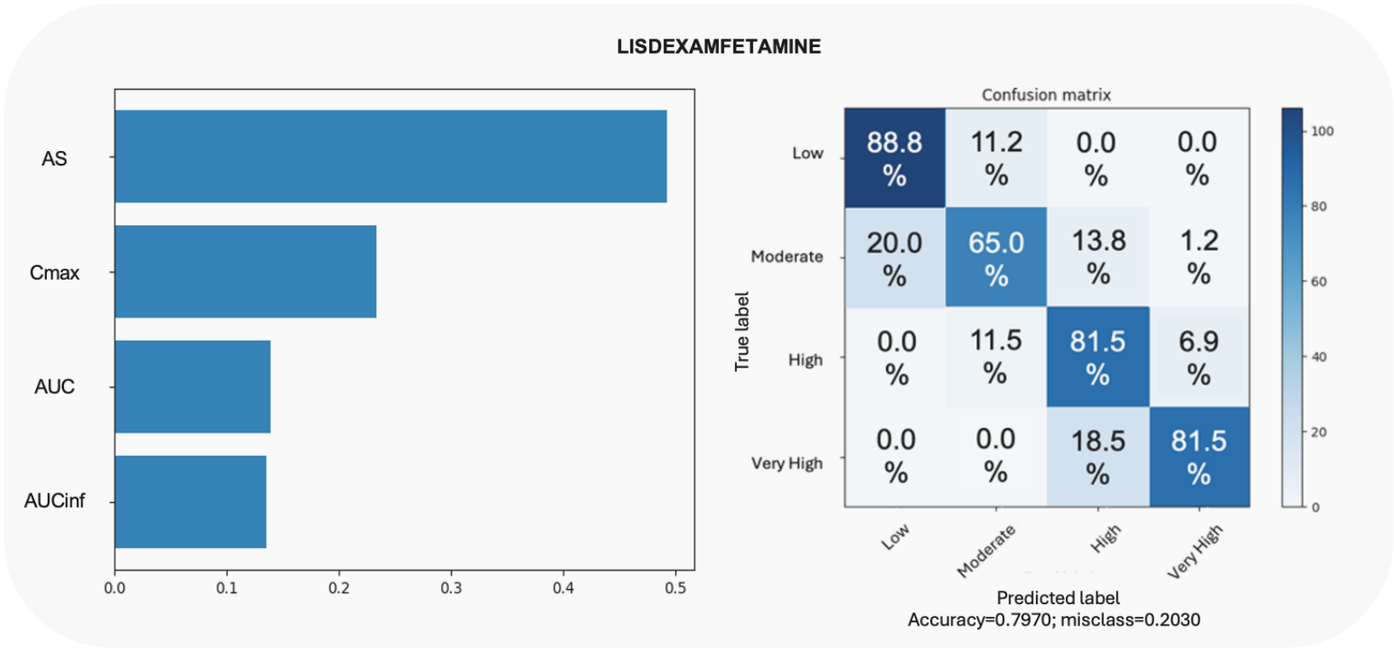
Random Forest was used for supervised learning, while **Principal Component Analysis** and **Hierarchical Clustering** were used for unsupervised learning, alongside **Artificial Neural Networks**.

3. Results



Principal Component Analysis

AS and Tmax exhibit contrasting kinetic behaviors, as AS increases, reflecting faster absorption, Tmax decreases. Therefore, **AS can effectively capture changes in absorption kinetics**.

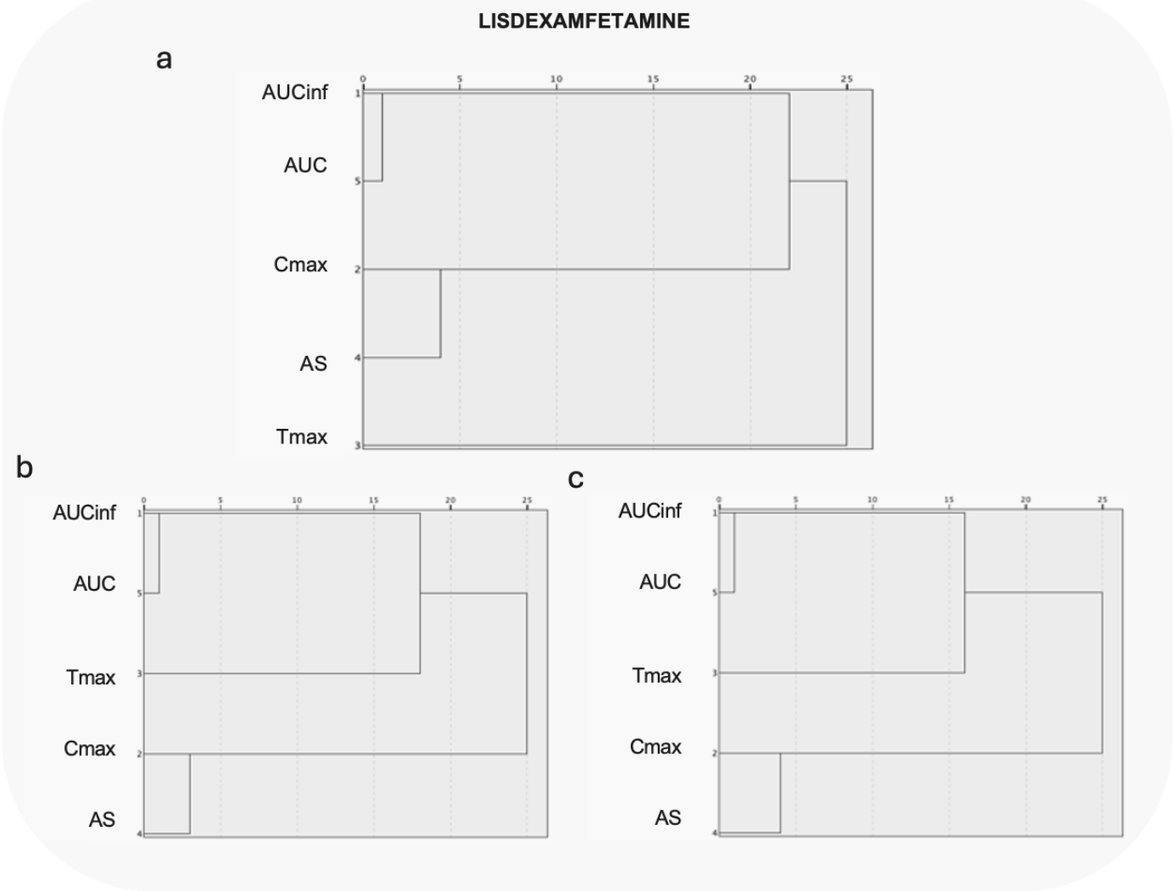


Random Forest

Cmax exhibited a lower contribution to Tmax with a variable importance score of 23.32%, **less than half the importance score of AS**.

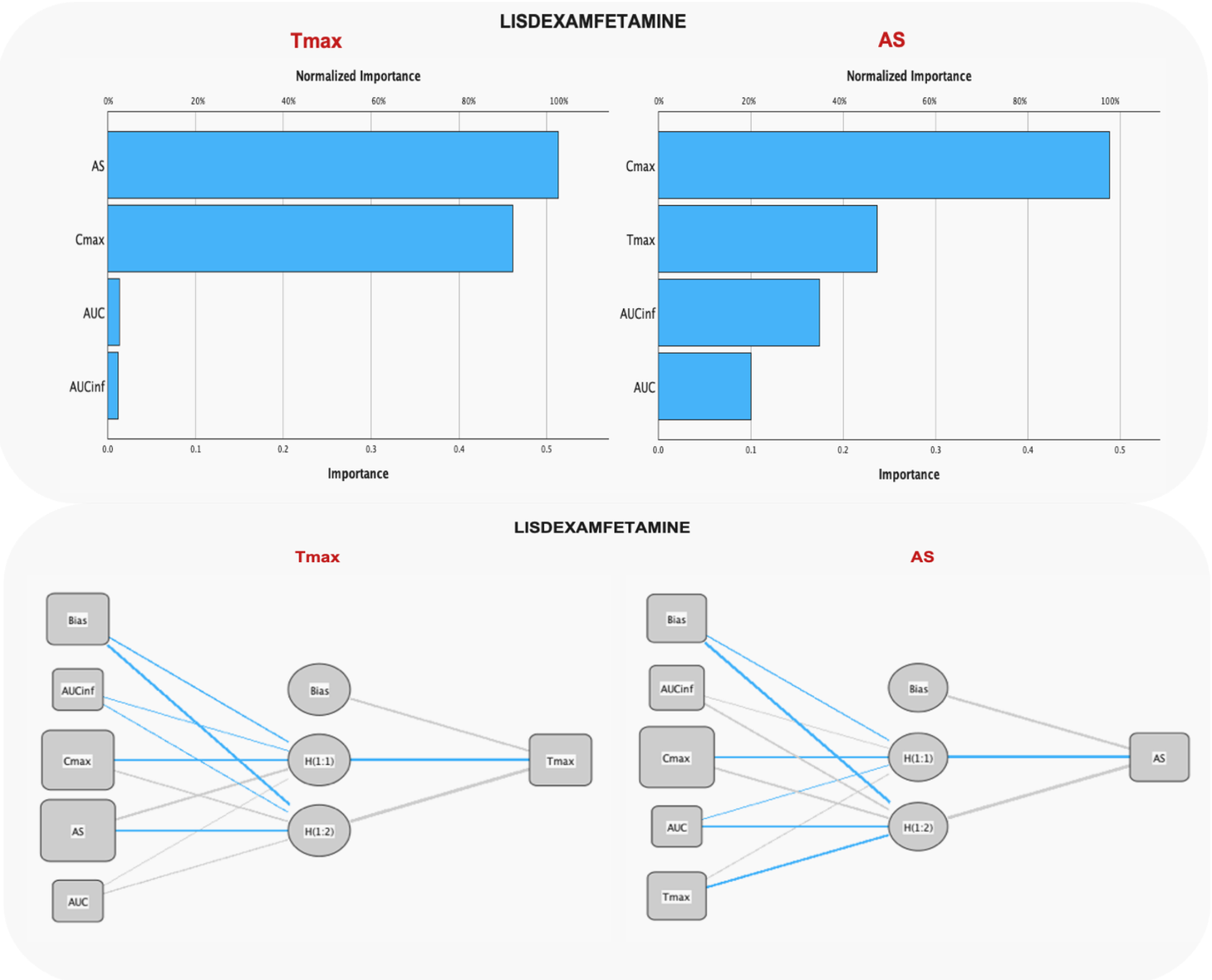
3. Results

Hierarchical Clustering



AUC and AUCinf have the closest relationship, consistently forming the first cluster regardless of the linkage type used. **AS and Cmax** are the second to form a cluster in all linkage methods, suggesting a notable **similarity between them**.

3. Results

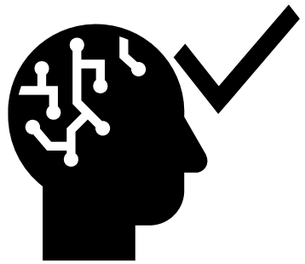


Artificial Neural Networks

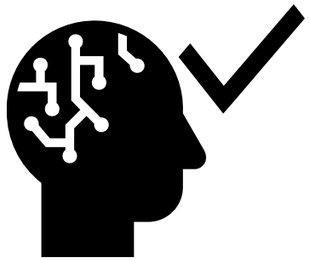
AS is the most important parameter for predicting Tmax, followed closely by Cmax, which also holds significance in predicting Tmax. AUC and AUCinf exhibit nearly zero importance in predicting Tmax. **Cmax holds more importance in predicting AS**, with Tmax being the second most important parameter, having roughly half the importance of Cmax.

All the methods described above were also applied to the remaining four drugs, and they produced results similar to those observed with lisdexamfetamine.

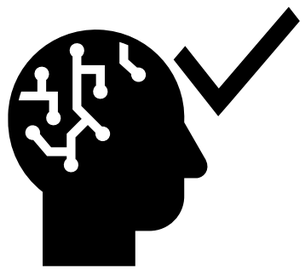
4. Conclusions



All the ML models consistently demonstrated that **AS is more effective in capturing changes in absorption kinetics**, as it correlates strongly with Tmax and accurately reflects the absorption rate across all tested drugs.



AS is calculated directly from the C-t data and exhibits the **best kinetic properties** compared to all other pharmacokinetic parameters.



AS could offer **a robust alternative to Cmax** and serve as a standard metric for assessing absorption rates in bioequivalence studies by regulatory agencies like the US FDA and EMA.

5. References

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