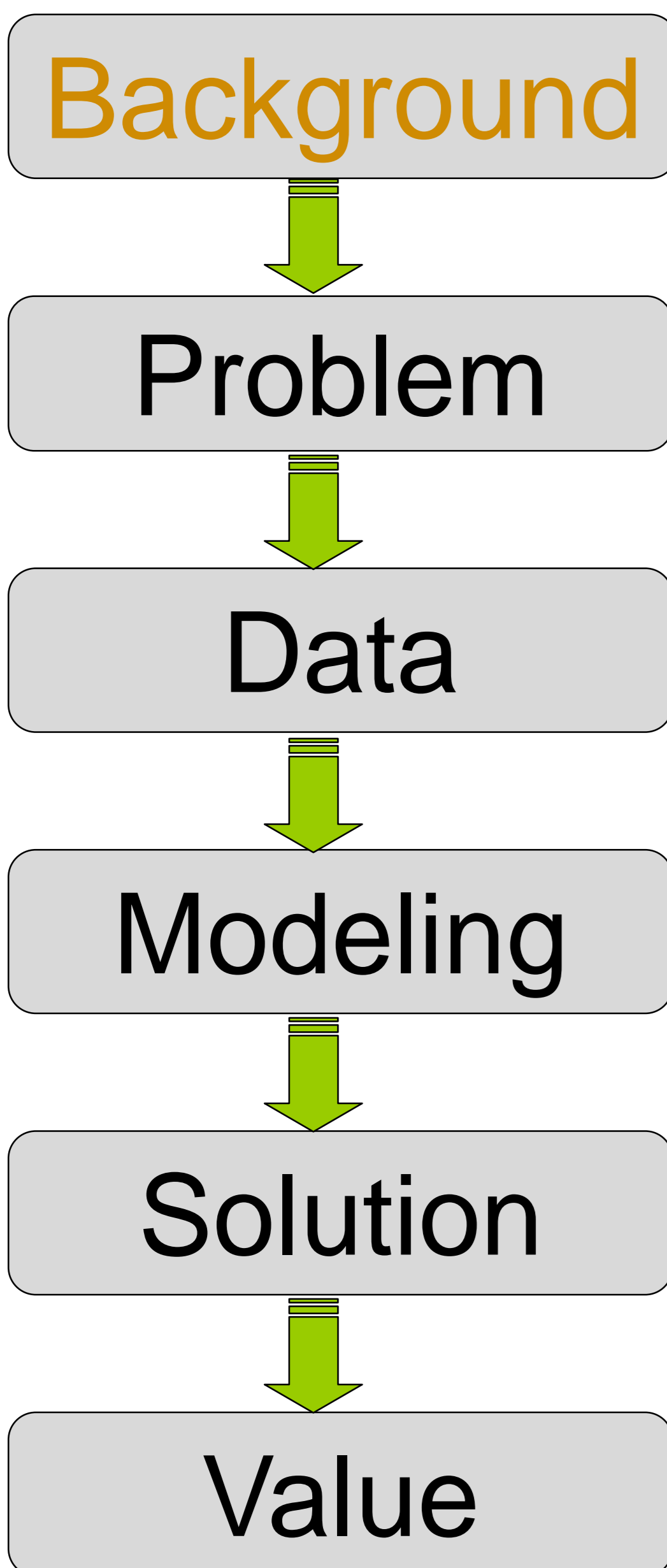
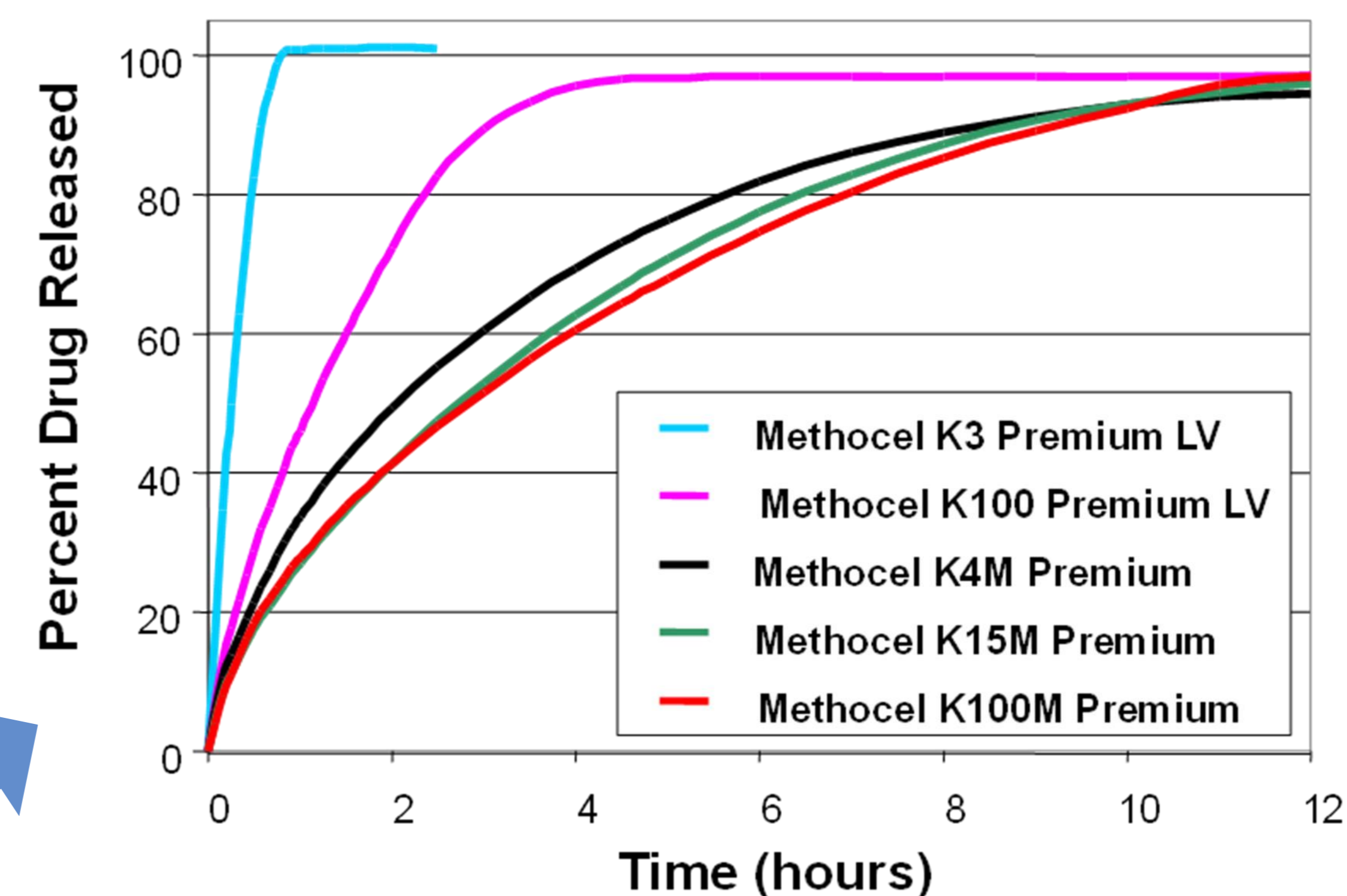
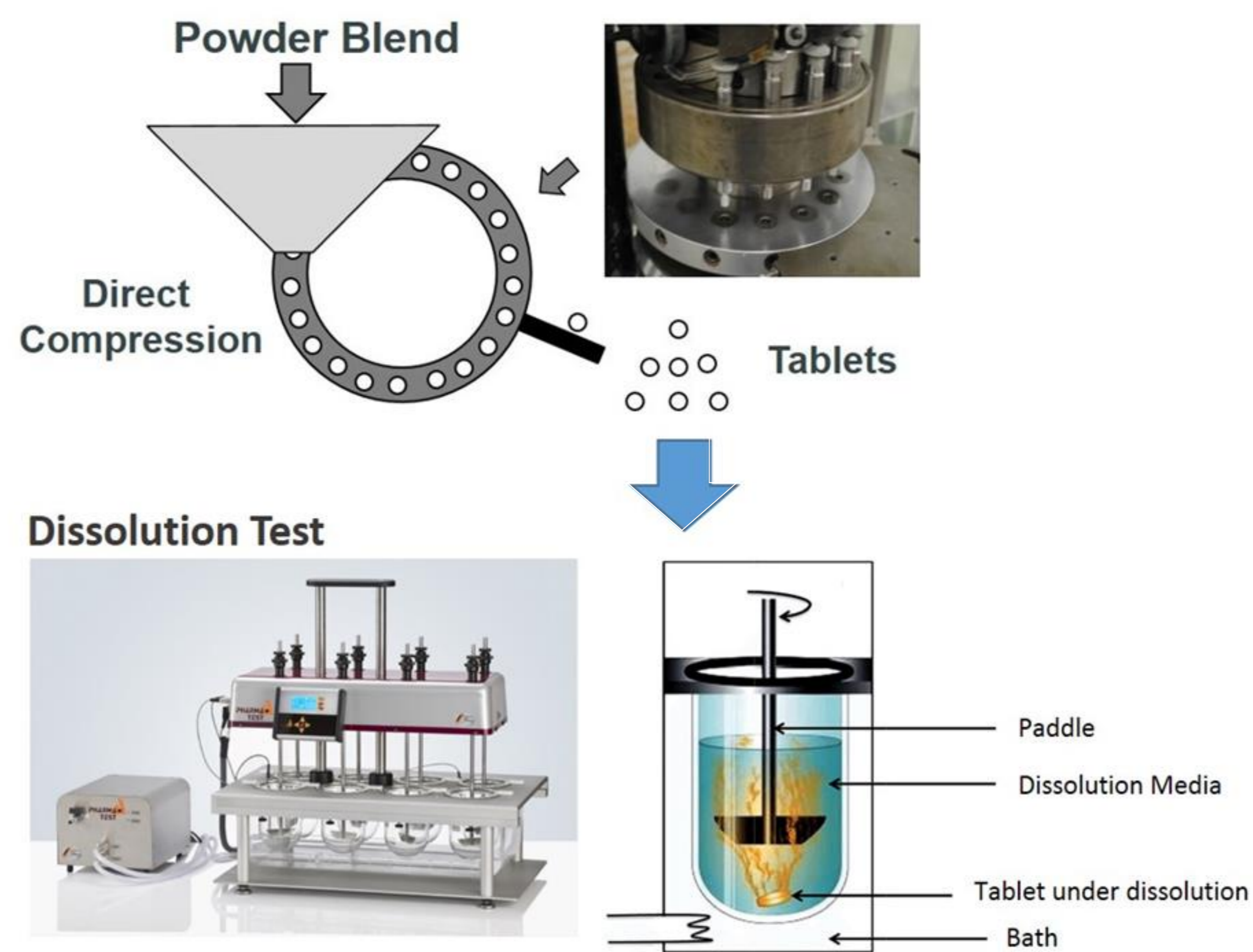


# Statistical Modeling of Drug Release Profile for HPMC Matrix Tablets

Wenzhao Yang, Jin Zhao, Jamie Curtis-Fisk, Karen Balwinski, True Rogers, and Shrikant Khot  
The Dow Chemical Company

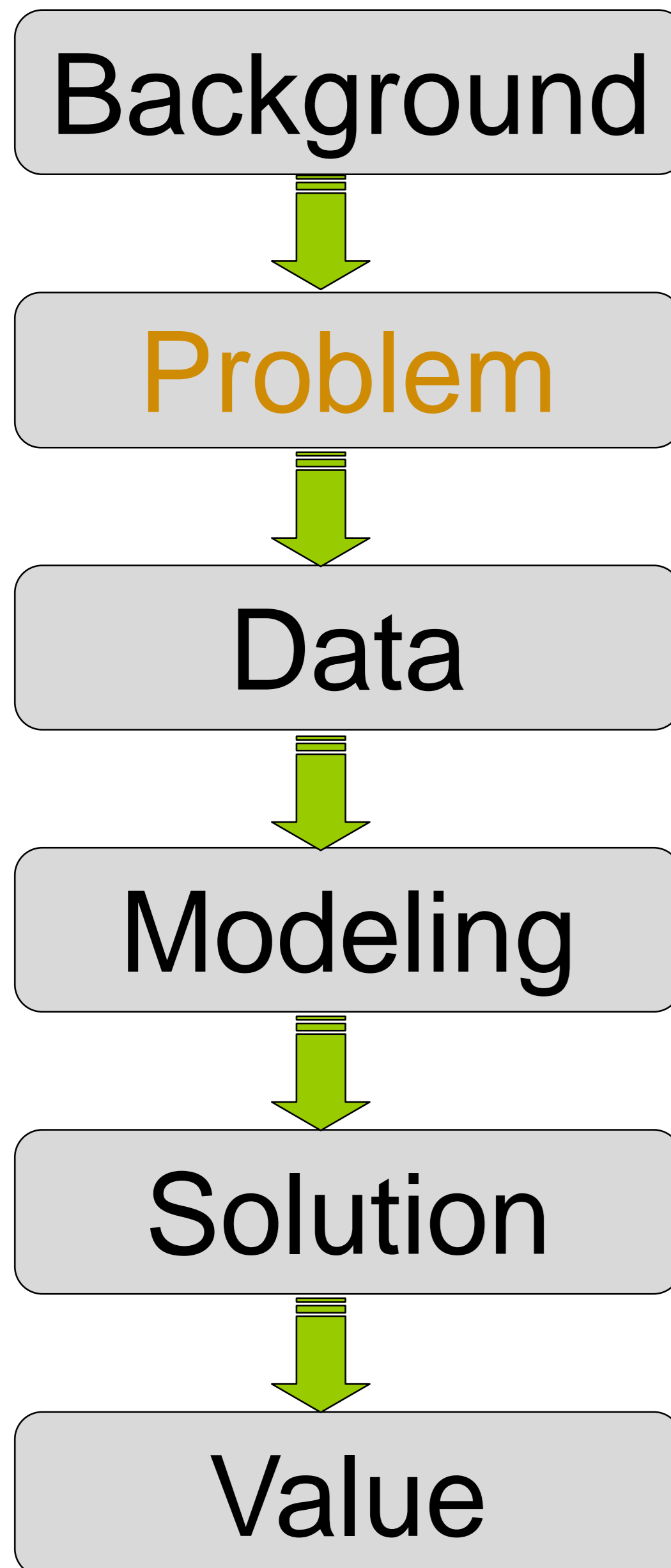


- **Hydroxypropyl methylcellulose (HPMC) matrix tablets** are a commonly used oral drug delivery system to modulate **drug release** over time

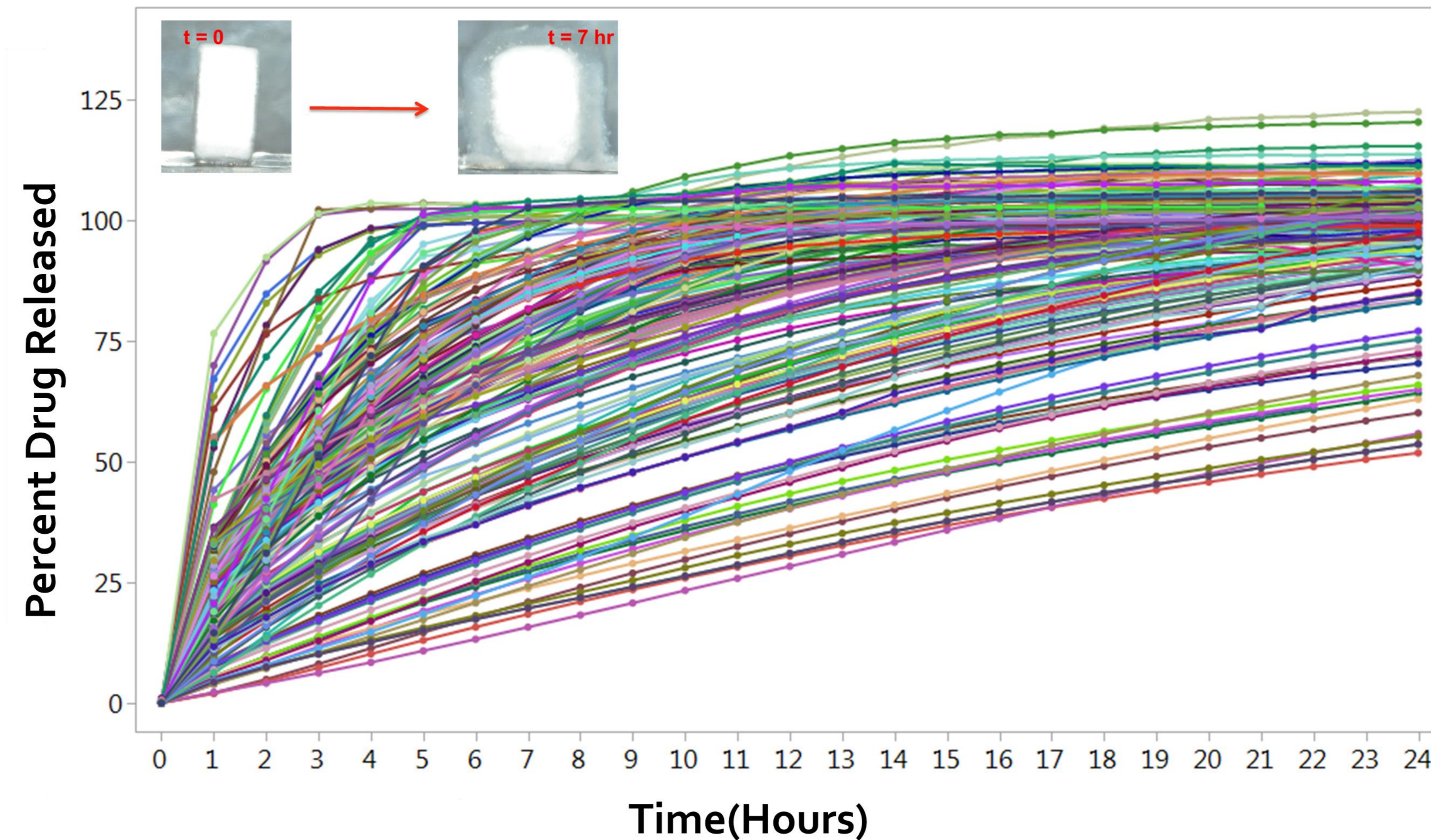


# Statistical Modeling of Drug Release Profile for HPMC Matrix Tablets

Wenzhao Yang, Jin Zhao, Jamie Curtis-Fisk, Karen Balwinski, True Rogers, and Shrikant Khot  
The Dow Chemical Company



- **Dow Case Study:** Develop and assess statistical models to aid pharmaceutical scientists with efficient and streamlined formulation design and *in vitro* drug release experimentation to deliver desired release performance



### Physical Characteristics (X)

- Kinetics and extent of polymer swelling and erosion
- Drug (API) dissolution, diffusion, and/or erosion through the polymer matrix

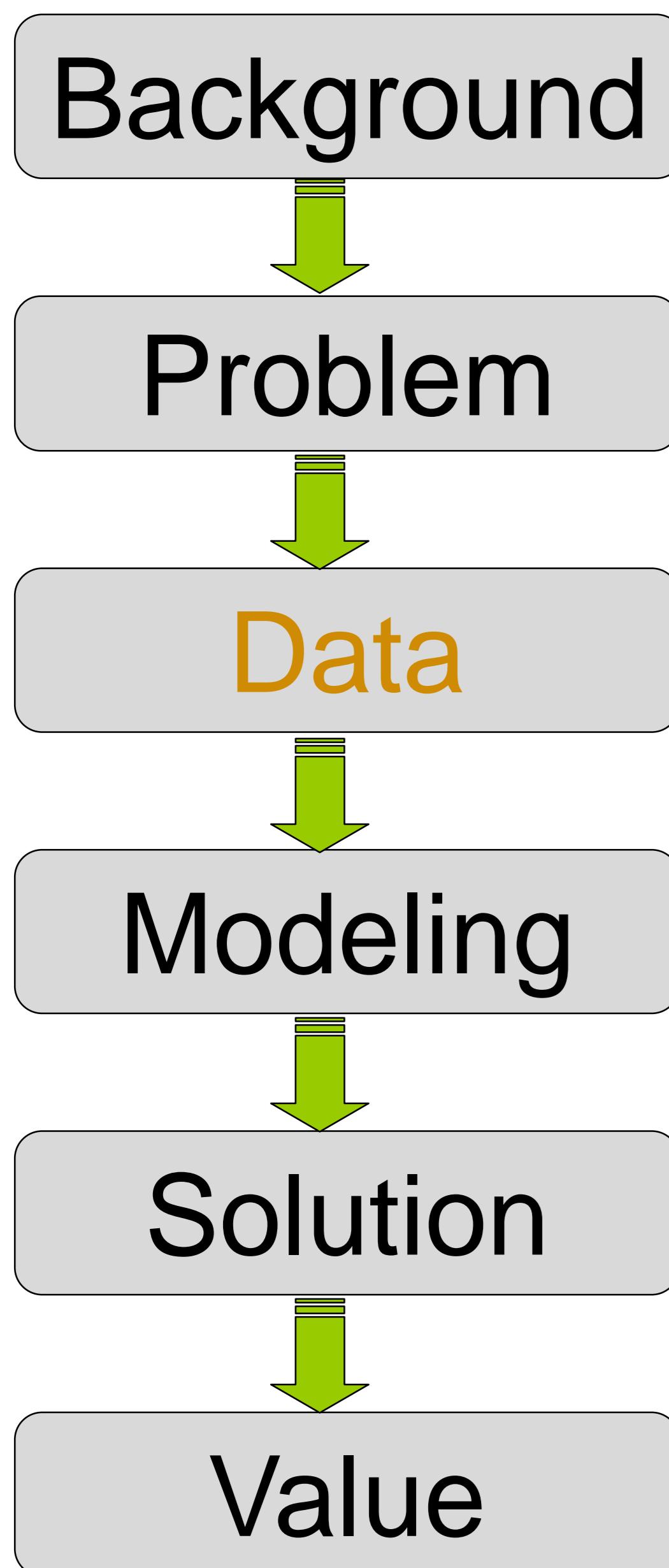
### Material Characteristics (X)

- Physiochemical properties of the rate-modifying polymer (e.g. HPMC)
- API physiochemical properties
- Formulation composition
- Manufacturing methodology



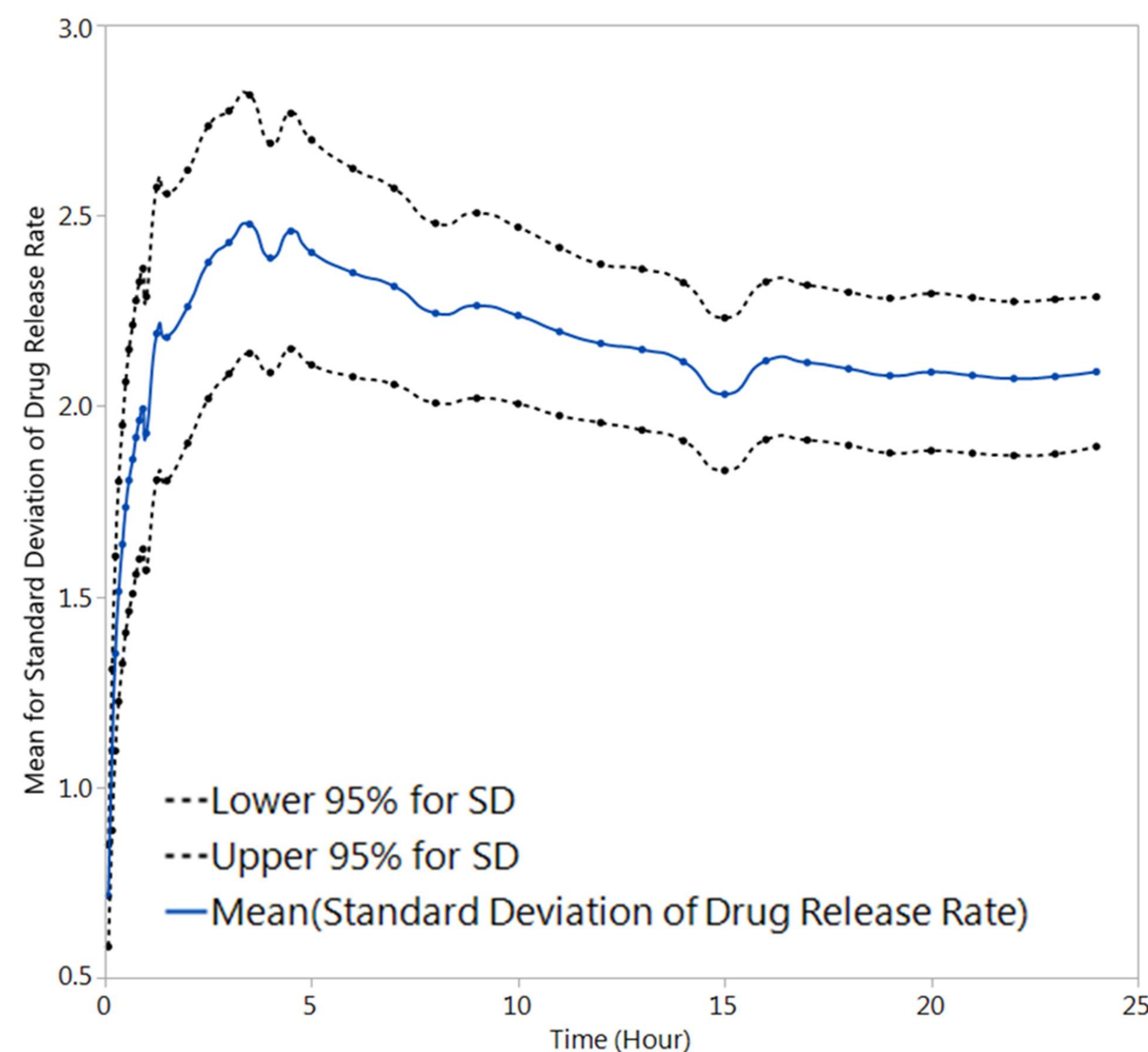
# Statistical Modeling of Drug Release Profile for HPMC Matrix Tablets

Wenzhao Yang, Jin Zhao, Jamie Curtis-Fisk, Karen Balwinski, True Rogers, and Shrikant Khot  
The Dow Chemical Company



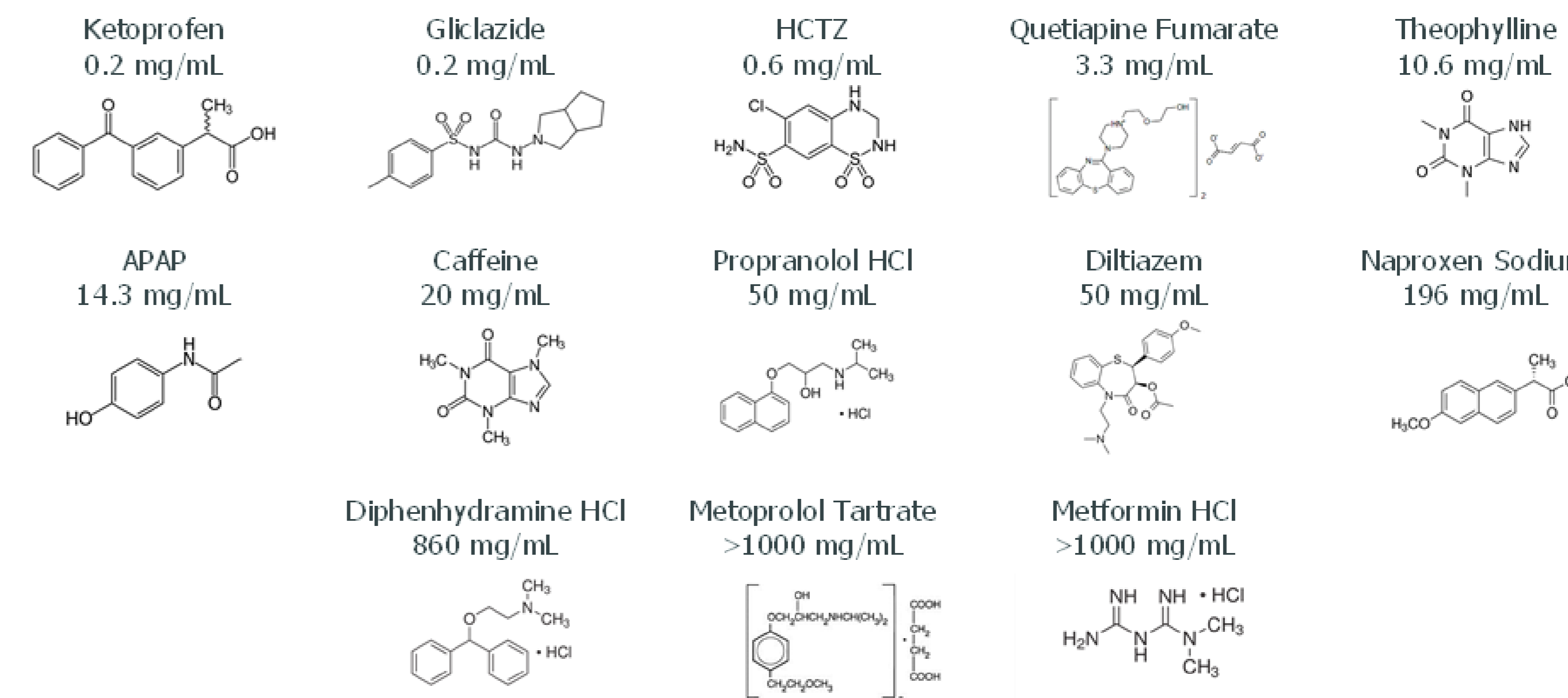
## • Drug release data quality (Y)

- Standard deviation (tablet-to-tablet variation)



## • Tablet Formulation (X)

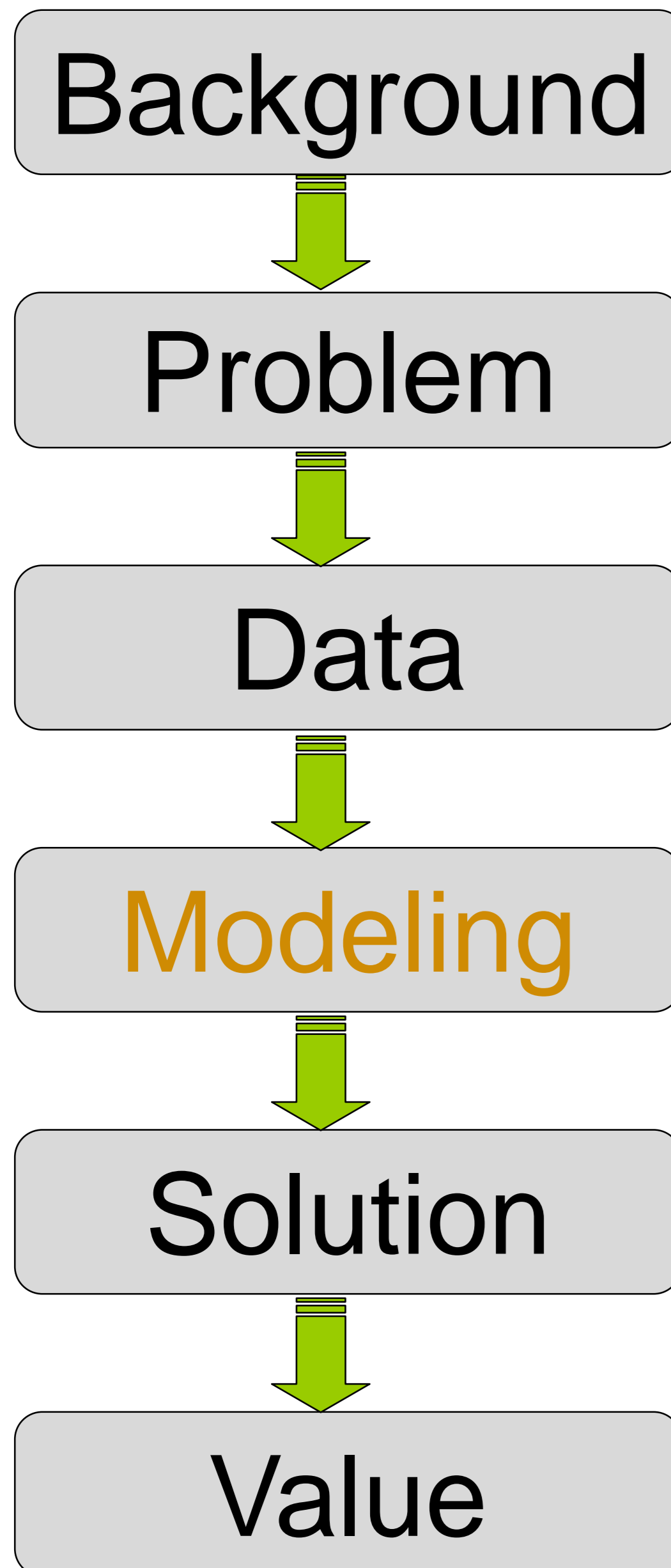
- Drug (API) with solubility from 0.2 to 1000 mg/ml
- Drug (API) concentration from 12.5 to 50 wt%
- HPMC grades of METHOCEL™ DC2 K100M, METHOCEL™ DC2 K4M, METHOCEL™ DC2 K100LV
- HPMC concentration from 20 to 40 wt%



# Statistical Modeling of Drug Release Profile for HPMC Matrix Tablets



Wenzhao Yang, Jin Zhao, Jamie Curtis-Fisk, Karen Balwinski, True Rogers, and Shrikant Khot  
The Dow Chemical Company



- **Linear mixed modeling (LMM)**

- A hypothetical model assuming 4 repeated measures over equally spaced time points

$$y_{ijk} = \mu + trt_i + time_j + trt \times time_{ij} + e_{ijk}$$

Time dependence

$$\text{var}(\mathbf{e}) = \mathbf{I} \otimes \mathbf{R}$$

AR(1)

$$\mathbf{R} = \begin{bmatrix} t_1 & t_2 & t_3 & t_4 \\ 1 & \omega & \omega^2 & \omega^3 \\ \omega & 1 & \omega & \omega^2 \\ \omega^2 & \omega & 1 & \omega \\ \omega^3 & \omega^2 & \omega & 1 \end{bmatrix} \sigma_e^2$$

- **Two stage Modeling (STM)**

- Korsmeyer-Peppas model with kinetic parameters  $(k, n)$

$$\text{Drug Release Rate}(C_t/C_0) = k t^n$$

Empirical models (Stepwise, PLS, LASSO and Neural Network) by fitting  $k$  and  $n$  to  $X$

$$\text{Drug Release Rate}(C_t/C_0) = K(X) t^{N(X)}$$

- Peppas-Sahlin model with kinetic parameters  $(b_1, b_2, m)$

$$\text{Drug Release Rate}(C_t/C_0) = b_1 t^m + b_2 t^{2m}$$

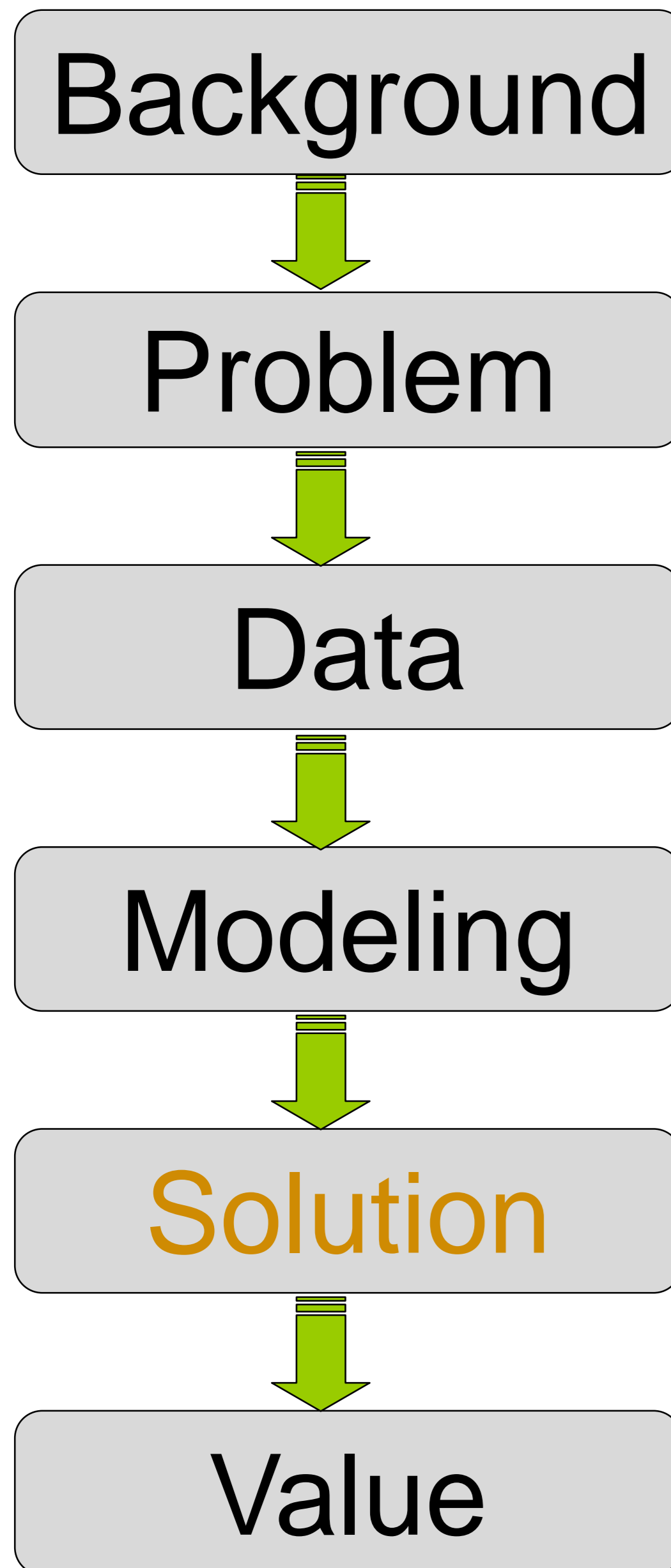
Empirical models (Stepwise, PLS, LASSO and Neural Network) by fitting  $b_1, b_2$  and  $m$  to  $X$

$$\text{Drug Release Rate}(C_t/C_0) = B_1(X) t^{M(X)} + B_2(X) t^{2M(X)}$$

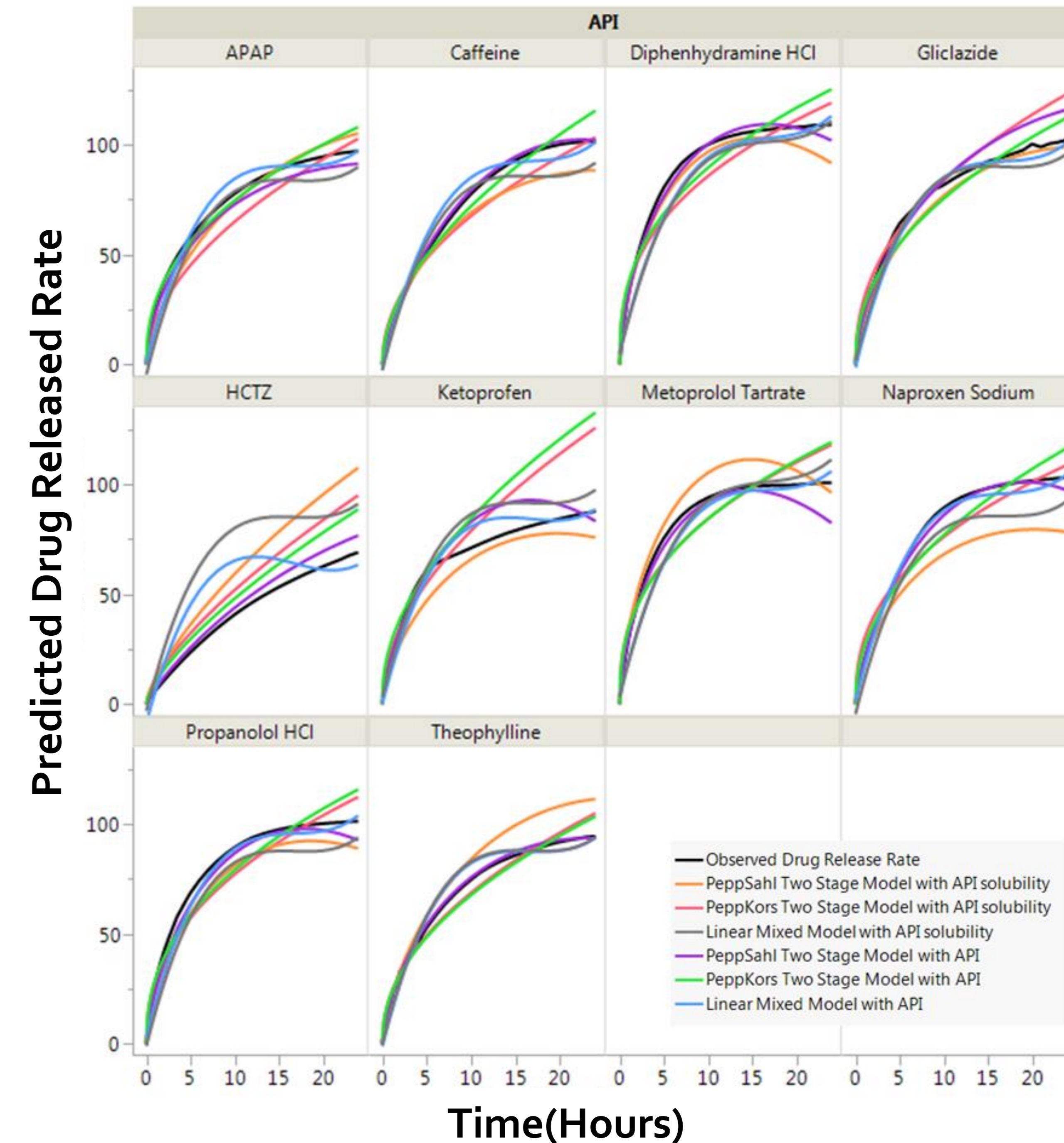


# Statistical Modeling of Drug Release Profile for HPMC Matrix Tablets

Wenzhao Yang, Jin Zhao, Jamie Curtis-Fisk, Karen Balwinski, True Rogers, and Shrikant Khot  
The Dow Chemical Company



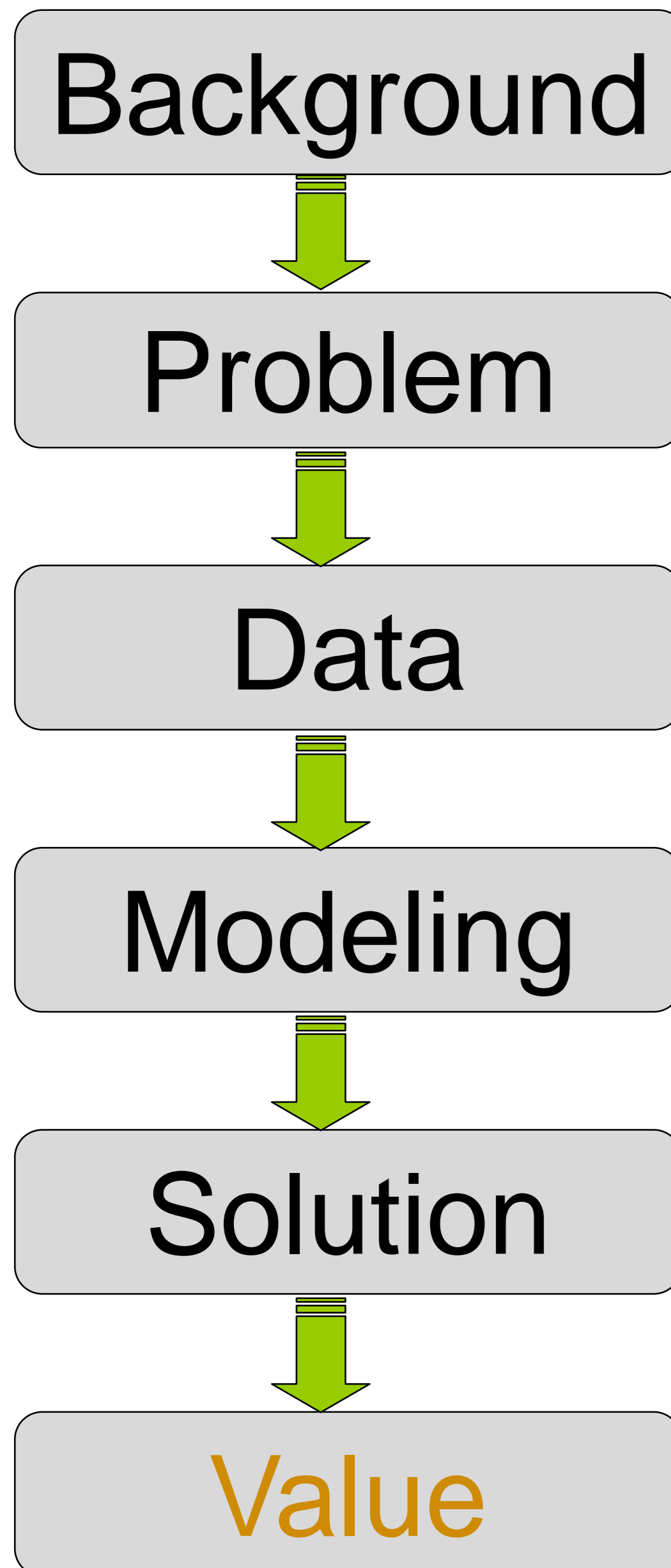
- The Peppas-Sahlin TSM with API has best agreement with the observed drug release profiles for most APIs except Gliclazide and Katoprofen
- The second best model is Korsmeyer-Peppas TSM with API solubility
- LMM has better overall prediction accuracy compared to the TSM at dissolution time > 2 hrs
- In addition to the drug characteristics (e.g. solubility), polymer viscosity grade and API concentration were found as key impacting factors



# Statistical Modeling of Drug Release Profile for HPMC Matrix Tablets



Wenzhao Yang, Jin Zhao, Jamie Curtis-Fisk, Karen Balwinski, True Rogers, and Shrikant Khot  
The Dow Chemical Company



- The business gained a better understanding about the key impacting factors for drug release profiles from statistical modeling
- Statistically defensible results obtained and promising predictive models identified to aid efficient and streamlined formulation design
- Dow gained significant experience in statistical modeling utilizing a complex system

