

Finding Rules for Controlled Release Tablets with FormRules

Background

Amongst the various formulation types for pharmaceutical preparations, the tablet is by far the most popular. Both immediate release and controlled release tablets can be produced.

£4,200.00 For controlled release, models exist which relate the *in vitro* release profile to *in vivo* behaviour. Consequently, a desired goal is to produce specific *in vitro* release profiles. Data have been obtained by Chen and coworkers (see e.g *Journal of Controlled Release* 59 33-41 (1999)) for release between 1 hour and 24 hours. Here, we have used these data to investigate which formulation variables control the release at different times, using **FormRules**.

FormRules is a unique software package, incorporating the best of artificial intelligence methodology and designed to be used by formulators. It is based on neurofuzzy logic, so combines the learning capabilities of neural networks with the intuitive linguistic capabilities of fuzzy logic, to give clear rules in *IF... THEN...* form. A variety of models are generated and tested automatically, showing unambiguously which input variables affect specific properties.

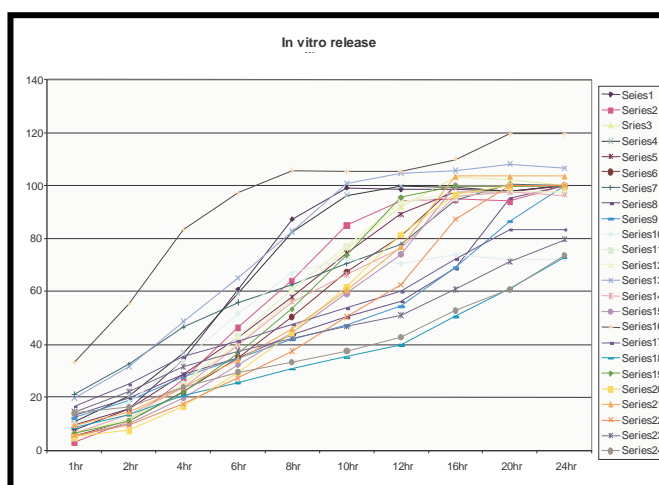
Controlled Release Formulations

In the Chen study, there were ten possible formulation variables:

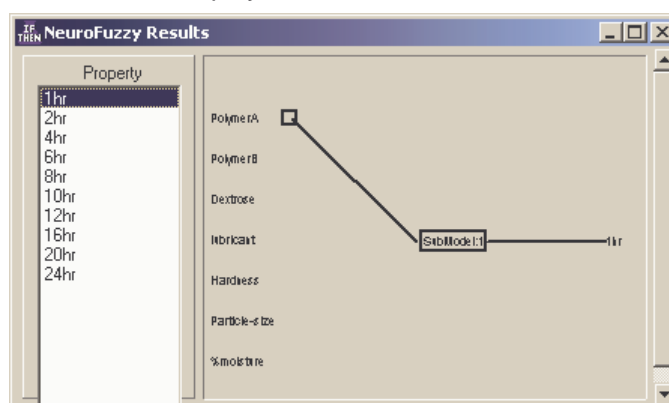
- ✕ Amount of Polymer A in each tablet
- ✕ Amount of Polymer B
- ✕ Amount of Dextrose
- ✕ Amount of Lubricant
- ✕ Tablet Weight
- ✕ Drug/(Polymer+Drug) ratio
- ✕ Polymer A/Polymer B ratio
- ✕ Tablet hardness
- ✕ Particle size
- ✕ % Moisture

Because Tablet Weight, and the two ratios, depend on other input variables, we omitted them from our study. Measured outputs were simply the amounts of release at different time periods. There were 24 different formulations in the Chen et al data.

As the results in the figure below show, some of the formulations have a high early release, while others release much more slowly. Our aim was to discover (with no prior knowledge) the difference between the two regimes.



The Graphical results from **FormRules** show clearly that release at shorter times is affected solely by the amount of Polymer A, while at long times it is controlled by the amount of Polymer B. In intermediate regimes, both polymers are important, and other variables like amount of lubricant and amount of moisture also play a role.

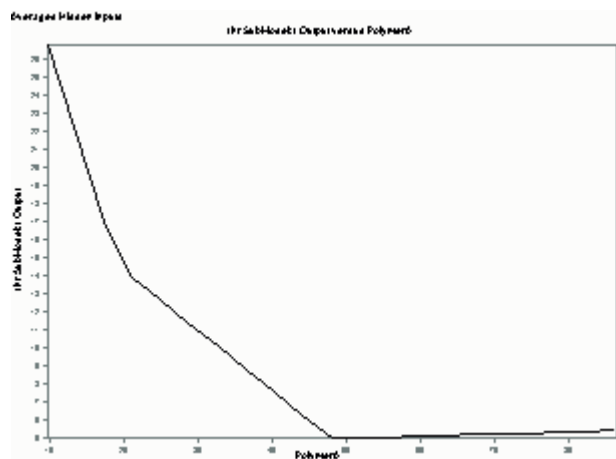


Graphical presentation of neurofuzzy system for 1 hr release

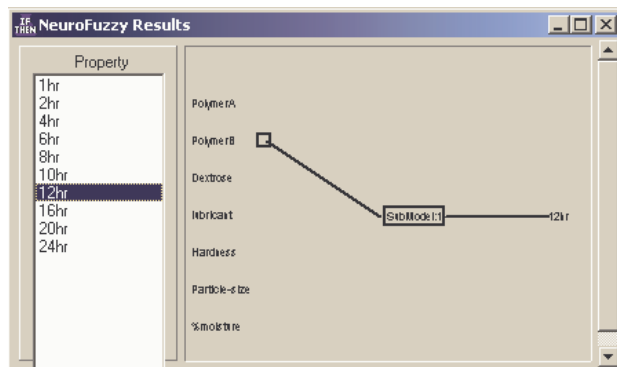
At 1 hour, the rules governing the release are:

- IF PolymerA is LOW THEN 1hr is HIGH (0.78)
- IF PolymerA is Low-Med THEN 1hr is LOW (0.62)
- IF PolymerA is Medium THEN 1hr is LOW (0.93)
- IF PolymerA is HIGH THEN 1hr is LOW (0.92)

Confidence values are given in parentheses. The form is roughly an exponential decrease, shown below for the 1 hour release.



Dependence of 1 hr release on amount of Polymer A

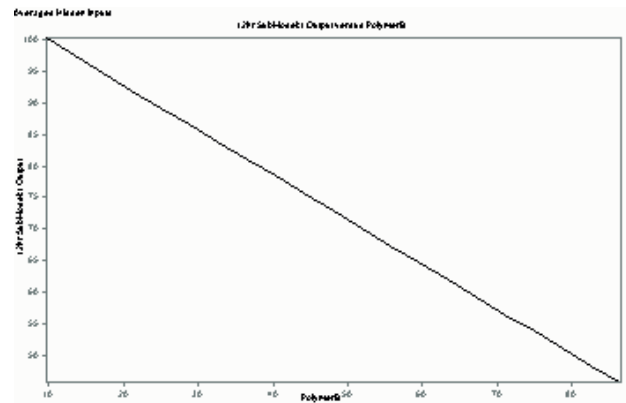


Polymer B controls the release at 12 hours (and at longer times)

For the 12 hour release (as mentioned above) only the amount of Polymer B is important. Here, the rules governing the release are relatively simple:

- IF PolymerB is LOW THEN 12hr is HIGH (0.92)
- IF PolymerB is HIGH THEN 12hr is LOW (0.91)

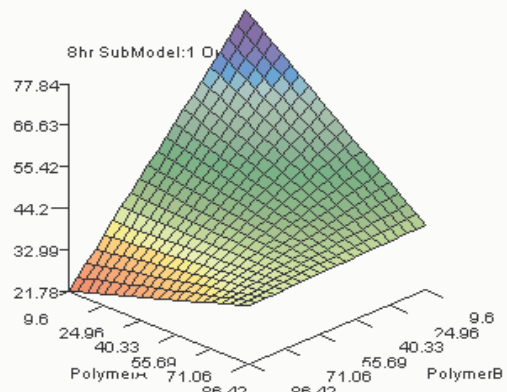
There is a linear relationship showing a decrease in release time with increasing amount of Polymer B, as the figure below shows.



Release time decreases linearly with the amount of Polymer B, for 12 hour release

Finally, as the figure and rules below show, amounts of both Polymer A and Polymer B affect the release at intermediate times – here, 8 hours.

8hr SubModel:1 Output versus PolymerB versus PolymerA



- IF PolymerB is LOW AND PolymerA is LOW THEN 8hr is HIGH (0.75)
- IF PolymerB is LOW AND PolymerA is HIGH THEN 8hr is LOW (0.76)
- IF PolymerB is HIGH AND PolymerA is LOW THEN 8hr is LOW (1.00)
- IF PolymerB is HIGH AND PolymerA is HIGH THEN 8hr is LOW (0.79)

Conclusions

Even from only 24 experiments, **FormRules** has developed useful models showing which input variables affect the release at different time periods.

The rules generated are those which would be expected by experienced formulators, showing that the technique can be used confidently by relatively inexperienced formulators, and for new problems where experience is lacking.

For further information on FormRules, and applying neurofuzzy logic to your problems, contact us at the address below.