

Finding Rules for Controlled Release Beads with FormRules

Background

Many-particulate beads offer advantages over conventional immediate or controlled release forms, especially for drug combinations when the drugs are incompatible, or for releasing drugs at specific rates, with less likelihood in drug dumping. Membrane-coated drug loaded beads have a release profile that depends critically on the coating used. Understanding the interactions between key formulation and process variables is essential if beads that exhibit a specific release profile are desired.

One new technology that can be applied is neurofuzzy logic - a technique that combines the learning and adaptive capability of neural networks with the ability of fuzzy logic to express conclusions based on vague, ambiguous, incomplete and imprecise information. This technique is rapidly gaining acceptance in data mining applications - including formulation data sets, and is the underpinning technology in the **FormRules** program.

Formulation Data

Siva Vaithiyalingam and Mansoor Khan, publishing in the *International Journal of Pharmaceutics* **234** 179-193 (2002), present experimental results for verapamil HCl released from beads coated by a pseudolatex. Their results were obtained by carrying out a 3-factor, 3-level central composite face-centred design. The three input variables were:

- coating weight gain
- duration of curing
- amount of plasticizer

An earlier study by Vaithiyalingam had identified these as important variables. Coating weight gain took the values 8%, 11% and 14%. Duration of cure was 24 hours, 36 hours, or 48 hours. Amount of plasticiser was chosen to be 60%, 90%, or 120%.

Outputs were the cumulative amounts of verapamil HCl released over 12 hours, at specific time points 2, 4, 6, 9 and 12 hours.

We have imported the published data directly into **FormRules**, and have used the neurofuzzy technique to examine the data.

Models for Multi-particulate Beads

FormRules can use all 16 data points, and tries out a variety of models. Each is assessed by a Model Assessment Criterion to balance the complexity of the model against the goodness of fit to the data. We found a good fit with the default Structural Risk Minimization (SRM), with an adjustable C_1 parameter of 0.8.

R^2 values (which show how well the model fits the data) are generally above 96%, except that for the 9-hour release where it is 85%. This value is still sufficiently high for the model to be trustworthy. More complex models, with higher R^2 values, can be created using the Minimum Descriptor Length model assessment criterion - however, with only 16 data points (including one repeat at the centre) there is a risk of 'overtraining', whereby the model starts to learn the noise in the system. The rules also become very complicated as the model's complexity increases.

With the relatively small amount of data, and with the simple SRM models, no interdependencies in the input variables were detected, as shown in Figure 1. If an interdependency had been discovered, then two input variables would have interacted in a single submodel, but here each submodel is affected by only one input variable.

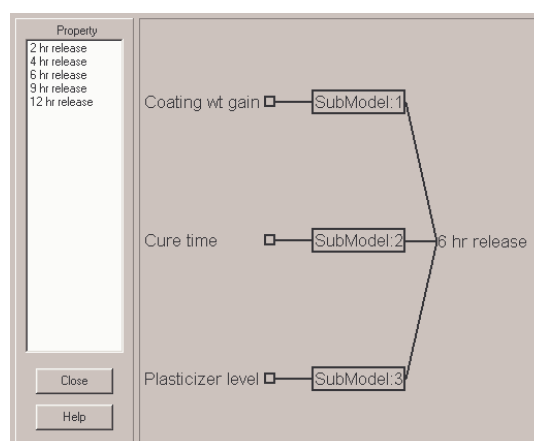


Figure 1. All three inputs affect the 6-hour release, but there are no interactions between them since each contributes through a separate sub-model

At each particular time point, all of the variables affected the amount of drug released.

Rules for Multi-particulate Beads

The rules for the 2-hour release (using the SRM models) are shown in Table 1.

IF Coating wt gain is LOW	THEN 2 hr release is HIGH (1.00)
IF Coating wt gain is HIGH	THEN 2 hr release is LOW (1.00)
IF Cure time is LOW	THEN 2 hr release is HIGH (0.92)
IF Cure time is HIGH	THEN 2 hr release is LOW (0.89)
IF Plasticizer level is LOW	THEN 2 hr release is LOW (0.76)
IF Plasticizer level is HIGH	THEN 2 hr release is HIGH (0.79)

Table 1. Rules for 2-hour release. Values in parentheses are confidence levels.

Similar rules apply for the other properties, as shown for 9-hour release in Table 2.

IF Coating wt gain is LOW	THEN 9 hr release is HIGH (1.00)
IF Coating wt gain is HIGH	THEN 9 hr release is LOW (1.00)
IF Cure time is LOW	THEN 9 hr release is HIGH (0.79)
IF Cure time is HIGH	THEN 9 hr release is LOW (0.68)
IF Plasticizer level is LOW	THEN 9 hr release is LOW (0.70)
IF Plasticizer level is HIGH	THEN 9 hr release is HIGH (0.81)

Table 2. Rules for 9-hour release.

Here, the rules have exactly the same format as those in Table 1. However, the values of LOW and HIGH depend on the particular values taken from the data, as Figures 2 and 3 show.

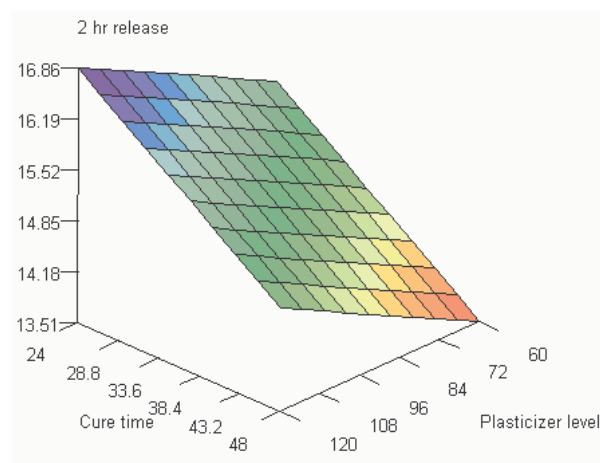
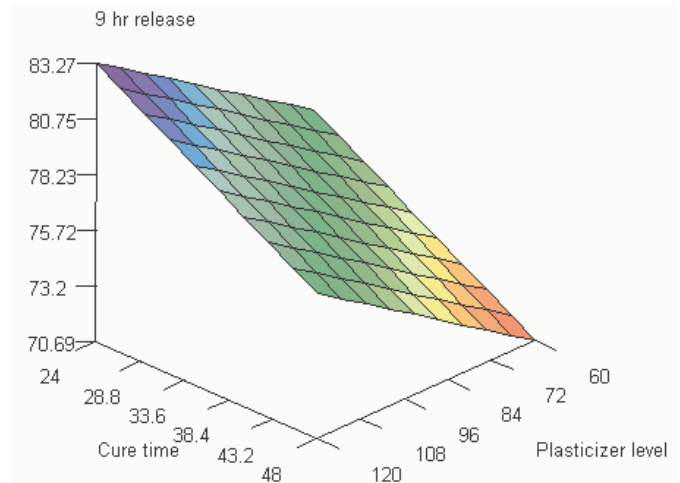


Figure 2. 2 hour release as function of Cure Time and Plasticizer level

Combining the sub-models into one model shows this more clearly. In Figure 2, which

corresponds to 2-hour release, the values for the combined submodels are between LOW of 13.5 and HIGH of 17. For Figure 3, they lie between LOW of 70.7 and HIGH of 83.3, again corresponding to the experimental data used to train the models.



We also note, from tables 1 and 2, that it can be seen immediately that adding plasticizer will increase the amount of release at each time point, in line with intuitive expectations.

Conclusions

Using a relatively small data set, **FormRules** has been able to extract the underlying relationships and rules governing the release profiles of multi-particulate beads.

With this information, the formulator can see immediately which inputs affect the release at specific times and how they do so, thereby developing new formulations that match desired release profiles.

The knowledge discovered directly from the data is consistent with that expected by experienced formulators.

More input data (i.e. more formulations and corresponding release profiles) would lead to more complex models and more complicated rules.

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

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